Synthesis of Cyclopropane-Fused 1,5-Diazocin-2-ones via Metal-Templated Intramolecular Addition of Nitrogen Nucleophiles to Pre-Generated Cyclopropenes

By

Jonathon Paul Matheny

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Chairperson: Prof. Michael Rubin

Prof. Jon Tunge

Prof. Paul Hanson

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The thesis committee for Jonathon Paul Matheny certifies that this is the approved version of the following thesis:

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Michael Rubin (Chairperson)

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Abstract

This thesis is concerned with the development of methods by which to access compounds possessing the 3,4-cyclopropane-annulated 1,5-diazocin-2-one scaffold. The methods described herein are based on the intramolecular nucleophilic addition of nitrogen nucleophiles to the cyclopropene double bond in a direct 8-membered cyclization. This method allows for access to previously-unknown diazocines of their type – namely, 1,5-diazocin-2-ones possessing fusion to a cyclopropane moiety. The described method allows for potential diversification of the cyclic products via a modular approach to the linear precursors which affords the possibility to easily explore new chemical space by the variation of simple building blocks.

Chapter one provides a review of the known methods by which to synthesize 1,5-diazocin-2-ones. The chapter begins by highlighting the importance of members of this class of molecules as effective pharmaceutical agents and as drug candidates. Synthetic methods involving the direct 8-membered cyclization of linear precursors are then discussed – as well as their modes of activation. Furthermore, synthetic approaches to the scaffold by cycloaddition, transition metal-catalyzed tandem reactions, multicomponent reactions, and various rearrangements and fragmentations are discussed.

Chapter two describes the development of a synthetic pathway to the direct precursors to the cyclopropane-annulated 1,5-diazocin-2-one scaffolds that are the targets of the efforts of this project. Synthetic strategies are developed and improved upon in order to afford substrates that are relatively easy to construct and assemble in a modular fashion

Abstract (Continued)

so as to provide easy access to a plethora of new compounds having potentially interesting bioactivities.

Chapter three focuses on the strain release-driven cyclizations of the previously described precursors to afford the diazocinone scaffold of interest. The optimization of the reaction and tolerance of the method to the electronic nature of the various nucleophiles employed is discussed. This method is one requiring mild conditions by taking advantage of the high energy and electrophilicity of the cyclopropene moiety. Several novel diazocines are synthesized with the developed method.

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“It's only after we've lost everything that we're free to do anything.”

–Tyler Durden

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Chapter 1. The Synthesis of 1,5-Diazocin-2-ones

1.1 Introduction

Prior to the late 1960's, the 1,5-diazocin-2-one moiety (Figure 1) had received no attention from the synthetic community.[1] Compounds based on the homologous 7-membered scaffold (e.g. benzodiazepines) had already received much attention due to their then-newly discovered effects on the central nervous system of mammals where they were found to be potent anticonvulsive agents,[2] tranquilizers,[3] anxiolytics,[4] muscle relaxants,[5] and antiepileptics.[6] The wide range of biological importance of compounds possessing this 7-membered azalactam moiety sparked curiosity about whether the 8-membered homologues of such systems might exhibit similar, greater, or otherwise interesting biological activity. Over the decades following, interest in synthesizing these scaffolds grew ever more rapidly. A plethora of diverse synthetic pathways to novel 1,5-diazocin-2-ones emerged; and with them, structure-activity relationship studies confirming the biological importance of these molecules.

1.2 Nomenclature

The nomenclature, terminology, and numbering used in describing 8-membered azalactams such as 1,5-diazocinones is not highly uniform throughout the literature. As is the case with much of chemical nomenclature, certain names may refer to a very specific set of chemical species, while the very same name may be used elsewhere in the chemical literature in a more inclusive manner – sometimes referring to a large set of structures which all possess some common feature. The nomenclature surrounding azalactams is, at very least, less than perfectly conducive to understanding and clear communication. In

order to inoculate the reader against confusion and ambiguity, the nomenclature of so-called “diazocinones” in the context of this thesis will be discussed at the outset.

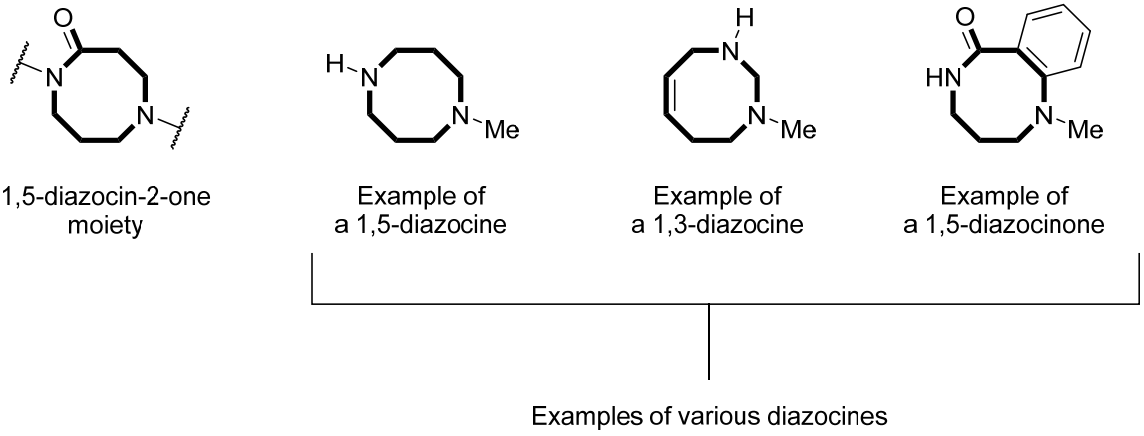


Figure 1: The 1,5-diazocine-2-one moiety alongside other diazocines.

This thesis is concerned with the synthesis of compounds possessing the 1,5-diazocin-2-one moiety; an 8-membered ζ–azalactam motif (Figure 1). Throughout this work, any chemical species containing this moiety may be referred to generally as a **diazocinone**, or even more generally – when the context is deemed to be clear – as a **diazocine**. The term diazocine refers to any 8-membered cycle with six carbon atoms and two nitrogen atoms – whether or not it contains a carbonyl. The term **diazoc*a*none** refers more specifically to **diazoc*i*nones** for which there is no unsaturation within the 8-membered ring itself. The terms that are used in this work have been chosen carefully with context and clarity as the guiding principles.

1.3 Occurrence in Nature and Biological Activity

Compounds containing the 1,5-diazocin-2-one moiety have scarcely been observed in nature.[7] Despite this, there has been a longstanding and consistently active synthetic

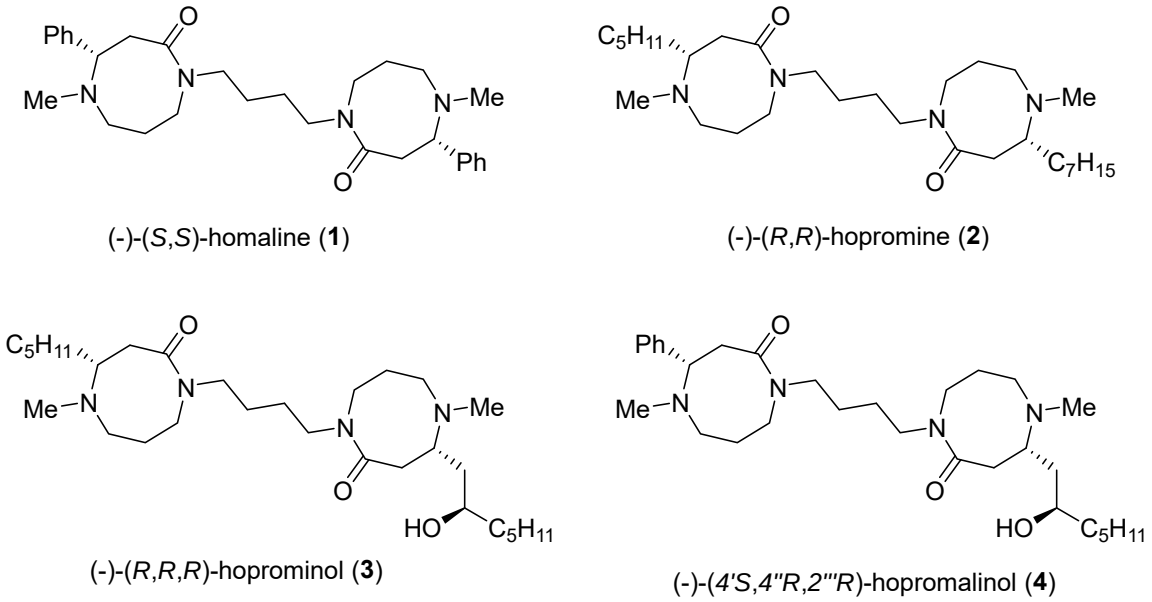


Figure 2: The four naturally-occurring members of the homalium alkaloid family.

interest in members of the naturally-occurring homalium alkaloid family (Figure 2). The four known naturally-occurring homalium alkaloids were isolated in the 1970's from the leaves of *Homalium pronyense* Guillaum – a plant species native to the forests of New Caledonia where it was first discovered. Though almost nothing is actually known about the true biogenesis of the homalium alkaloids, it often speculated that the alkaloids are biogenically-derived from spermine and the appropriate α,β-unsaturated fatty or cinnamic acids.[7,8] These unique bis-azalactams have been the targets of many synthetic efforts over the past three decades.[7]

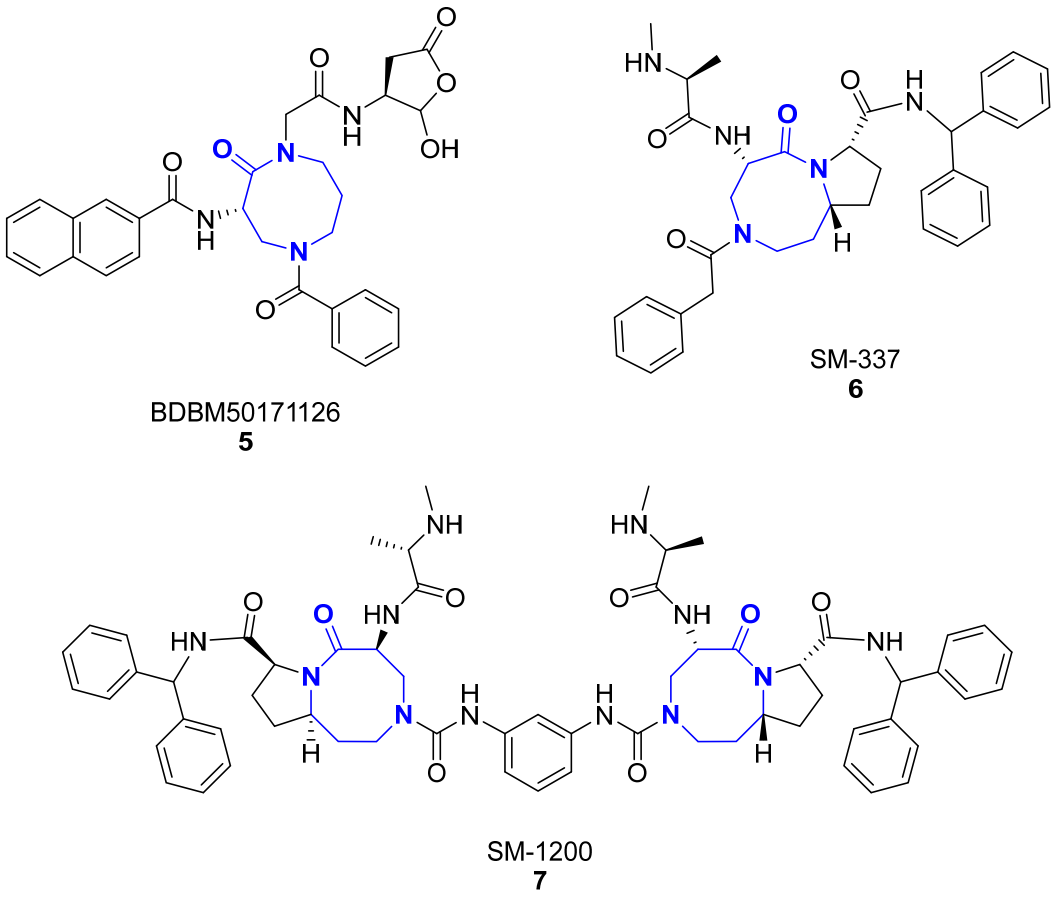


Figure 3: Drug candidates possessing the 1,5-diazocin-2-one moiety.

The 1,5-diazocin-2-one core is present in many potential and actual therapeutic agents (Figure 3). The diazocan peptomimetic **5** exhibits high levels of activity as a selective caspase-1 inhibitor (Casp-1 IC_{50} = 19 nM, THP-1 IC_{50} = nM); a relatively new class of pharmaceutical agents which are effective in the treatment of rheumatoid arthritis and, in addition, have shown promising anti-inflammatory and analgesic activity in animal models.[9,10]

The compound SM-337 (**6**) belongs to a family of conformationally-constrained mimetics of the endogenous IAP antagonist Smac (second mitochondria-derived activator

of caspases). Over the past decade, Smac mimetics have garnered increasing attention showing great potential as a new class of antitumor drugs. Compound **6** exhibits high potency as a cell growth inhibitor (IC_{50} = 31 nM) and in inducing apoptosis (100 nM, 24 h) in the MDA-MB-231 cancer cell line. This, coupled with its high oral bioavailability and excellent solubility in aqueous media, have prompted further optimization as well as *in vivo* testing.[11] A related compound (**7**) possesses the same 8,5-fused core as SM-122, but is joined to an identical unit via an acylated 4-phenylenediamine linker. Because of this two-unit structure, **7** is in a class dubbed "bivalent" Smac mimetics. Like its monovalent analogs, SM-1200 is designed to act as an IAP antagonist. Excellent levels of cell growth inhibition were observed in both MDA-MB-231 breast cancer (IC_{50} = 11.0 nM) and SK-OV-3 ovarian cancer (IC_{50} = 28.2 nM) cell lines. *In vivo* studies in mice impressively showed rapid and complete tumor regression. With the administration of 12 mg/kg per week for 4 weeks, 99% tumor regression was achieved in seven mice while six of the seven mice remained tumor-free for 27 days following the final dose.[12]

1.4 Synthetic Approaches Toward 1,5-Diazocin-2-ones

Medium-sized rings – and 8- to 10-membered rings, in particular – are difficult to synthesize via conventional methods of cyclization.[13] This is due in large part to the enthalpy cost incurred in the transition state as well as the increased enthalpy of the cyclic products relative to their linear precursors.[14] The effective synthesis of 8-membered 1,5-diazocin-2-ones via direct cyclization has been accomplished in some cases. This difficulty has stimulated the development of alternative methods for accessing the scaffold (Figure 4).

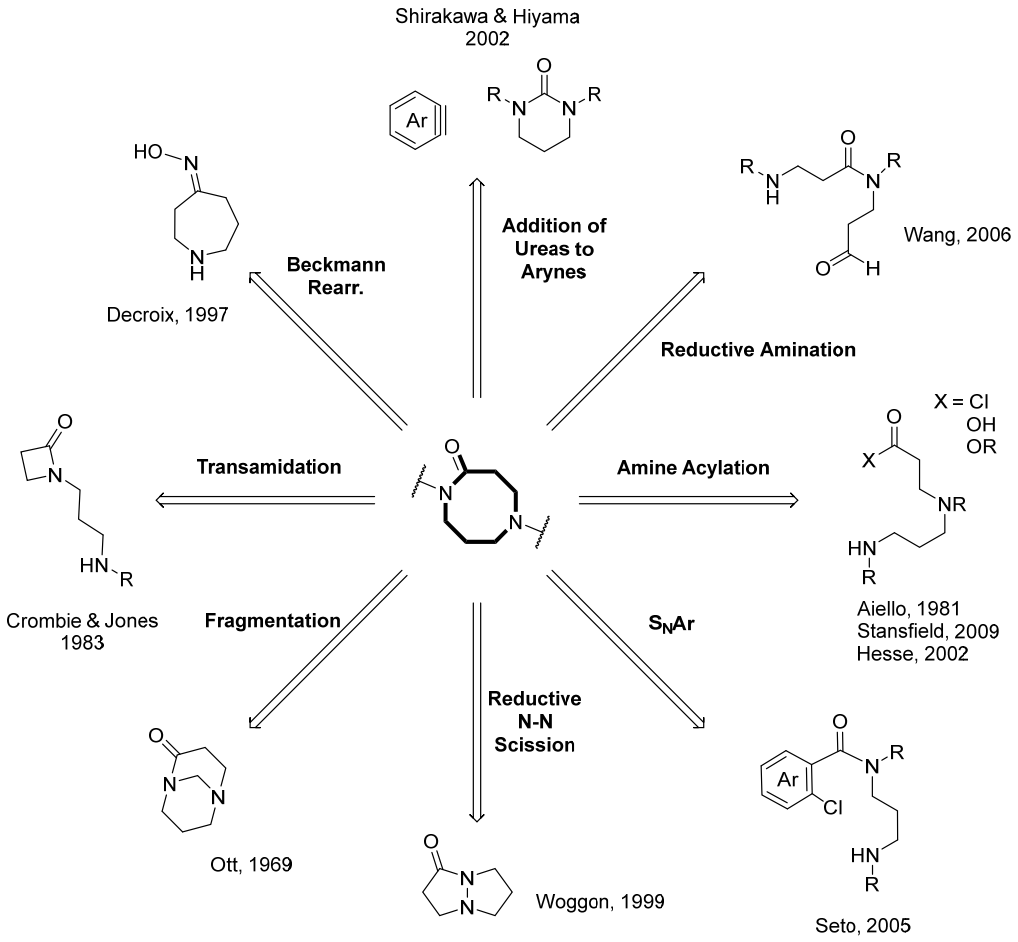


Figure 4: Several synthetic approaches to the 1,5-diazocin-2-one scaffold.

The rearrangements of existing ring systems, transamidative ring expansion, multi-component tandem reactions, and several other efficacious methods have emerged from these efforts. The remainder of this chapter provides an account of the conventional, as well as the more exotic, methods for the preparation of molecules containing the 1,5-diazocin-2-one moiety.

1.5 Direct 8-Membered Ring-Closure via Intramolecular Acylation of Amines

Accessing ζ-lactams and ζ-azalactams via 8-membered cyclization is often problematic due to the unfavorable enthalpic and entropic factors which do not plague systems of smaller (4-, 5-, and 6-membered), or in fact larger (12-membered and larger) size.[15] Though direct 8-membered cyclization could be considered the most straightforward route toward these heterocycles, it represents only a small portion of the published syntheses of 1,5-diazcin-2-ones.

1.5.1 Intramolecular Acylation of Amines

The successful direct 8-membered intramolecular acylation of amines to provide 1,5-diazocin-2-ones has been achieved in some cases. The success of these reactions varies greatly with varying substrates, and substrates often exhibit a strong or exclusive preference for a particular set of reagents and/or other conditions. Commonly employed reagents such as DCC, CMPI, thionyl chloride, the BOP reagent, and TBTU have all been shown to be effective in some cases – though no general conditions have been identified which are successful in general for the transformation.[16,17]

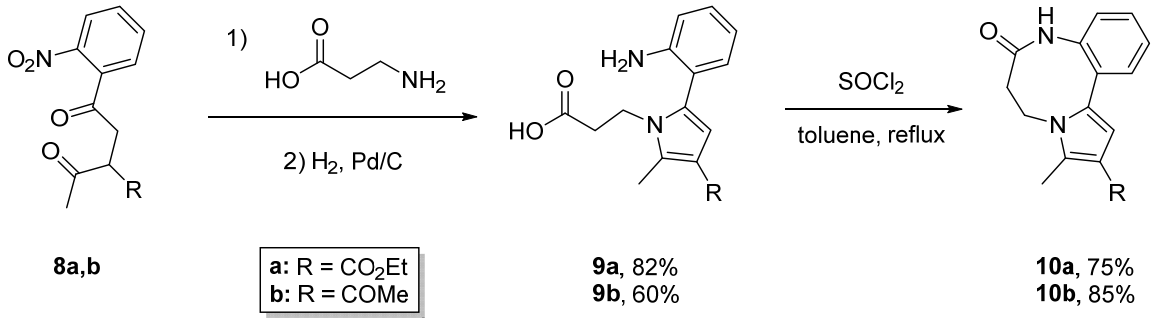
Activation of Carboxylic Acids

The activation of a carboxylic acid function toward intramolecular nucleophilic attack by an amine nitrogen is a common strategic starting point for the formation of 8-membered nitrogen heterocycles. A small number of examples are present in the literature.

In an effort to synthesize pharmacologically relevant homologues of then-recently reported potent CNS depressants of the benzodiazepine family, Aiello *et al*. prepared fused 3-ring 1,5-diazocenes **10** via activation of the carboxylic acid function of biaryl anilines **9**

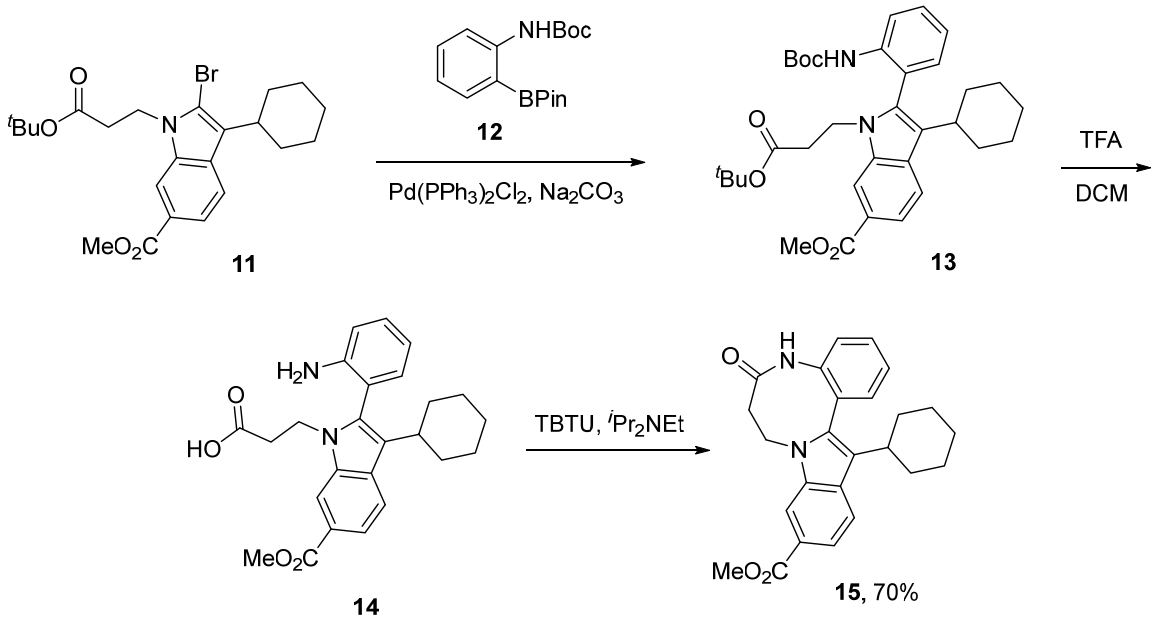
with thionyl chloride in good yields (Scheme 1).[18] To the knowledge of the author, this is the only report of a successful synthesis of 1,5-diazocin-2-ones employing thionyl chloride as a reagent for carboxylic acid activation.

Scheme 1



In 2008, Stansfield *et al*. reported the synthesis of tetracyclic indole **15** as a potential inhibitor of hepatitis C virus NS5B polymerase. Building upon a substituted indole scaffold, diazocine **15** was realized via late-stage 8-membered cyclization (Scheme 2).

Scheme 2

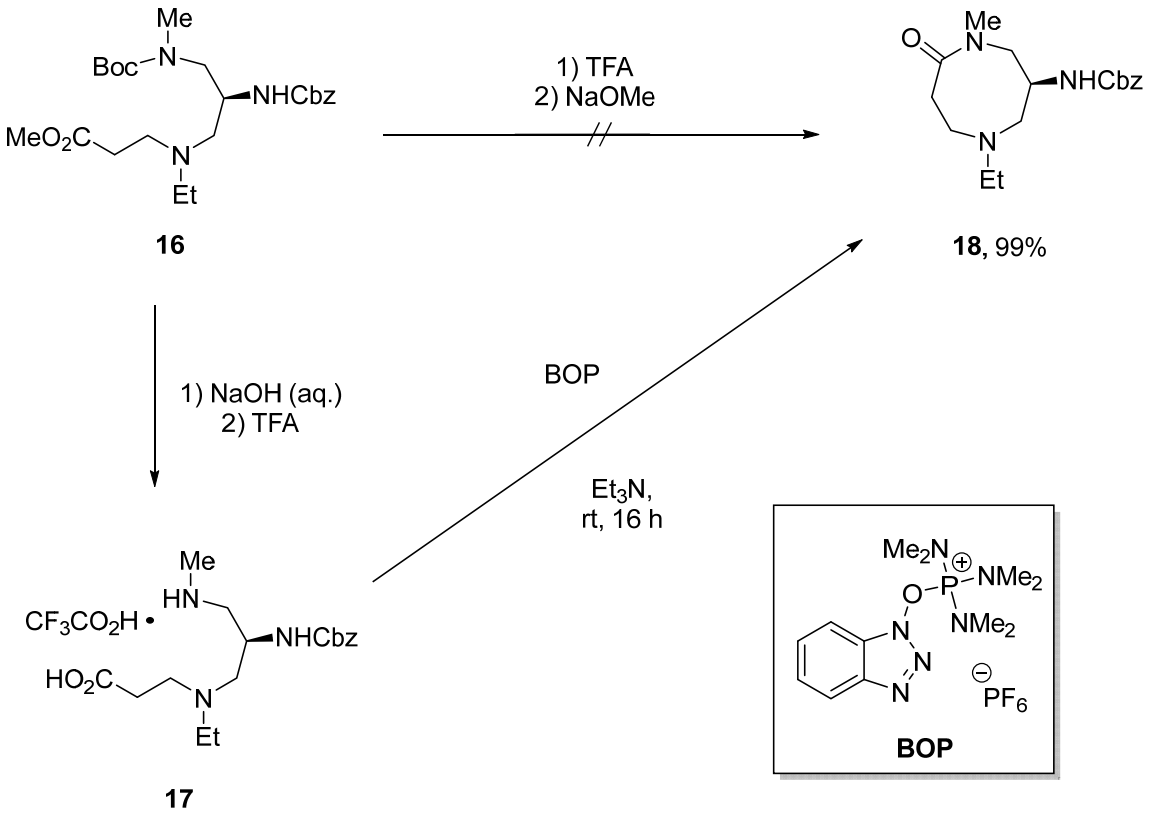


Activation of the carboxylic acid function of ζ-amino acid **14** was facilitated by peptide coupling reagent TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate). Direct 8-membered cyclization via nucleophilic attack of the aniline nitrogen on the activated acid function provided benzodiazocine **15**.[19]

Alkoxide-promoted intramolecular nucleophilic attack of amines on carboxylic esters to furnish ζ-lactams and ζ-azalactams is a known (albeit scarcely reported). While this chemistry is routinely employed in the conversion of esters to amides, in the context of the synthesis of 1,5-diazocin-2-ones it has not been successful. In an effort to synthesize saturated 7-amino-1,5-diazocinone **18,** Hirokawa *et al*. attempted the cyclization of protected amino ester **16** via Boc-deprotection with trifluoroacetic acid followed by treatment with sodium methoxide (Scheme 3). These conditions failed to provide the product. Aqueous hydrolysis of the ester function of **16** with sodium hydroxide and

subsequent treatment of the resulting amino acid (**17**) with the BOP reagent furnished the saturated chiral diazocine **18** in nearly quantitative yield.[16]

Scheme 3

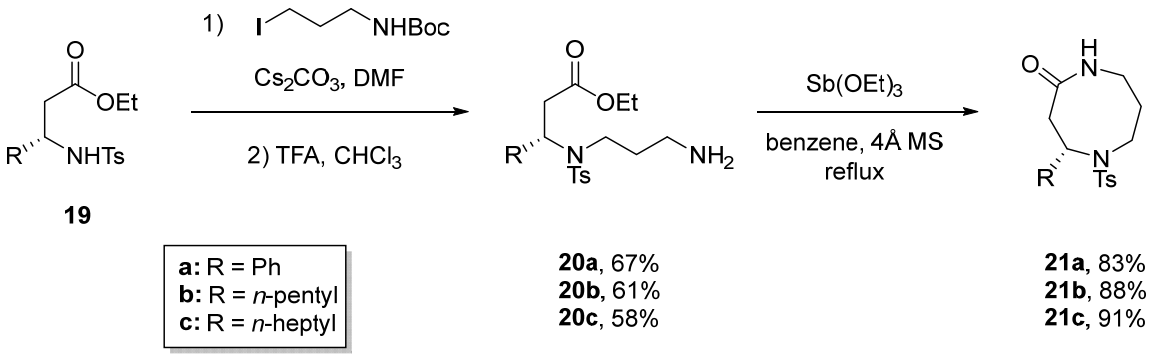


Azalactams containing no unsaturation in, or ring fusion to, the 8-memebered ring are generally considered to be greater synthetic challenges than their unsaturated counterparts as their linear precursors exhibit more degrees of freedom resulting in the amplification of unfavorable entropic factors of medium-sized ring closure.[20] This example of the cyclization of a saturated 1,5-diazocin-2-one **18** shows the BOP reagent to be effective, albeit in just a single case.

Metal-Templated Intramolecular Acylation

With the total synthesis of spermine alkaloids (–)-(*R*,*R*)-hopromine (**2**) and (±)-homaline (**1**) by Hesse *et al*. in 2002, a novel path to optically-active 1,5-diazocan-2-one cores was established via an antimony-templated cyclization (Scheme 4). Chiral *N*-sulfonyl-protected β-amino esters **19** were alkylated at the sulfonamide nitrogen with *N*-Boc-protected 1-iodopropylamine and subsequently converted into the corresponding free chiral amines **20** using trifluoroacetic acid. In screening conditions for the cyclization of ζ-amino esters **20**, the commonly-employed peptide coupling systems DCC/DMAP, 2-chloro-1-methyl-pyridinium iodide/Et_3N, and DPS, as well as mixed anhydride systems

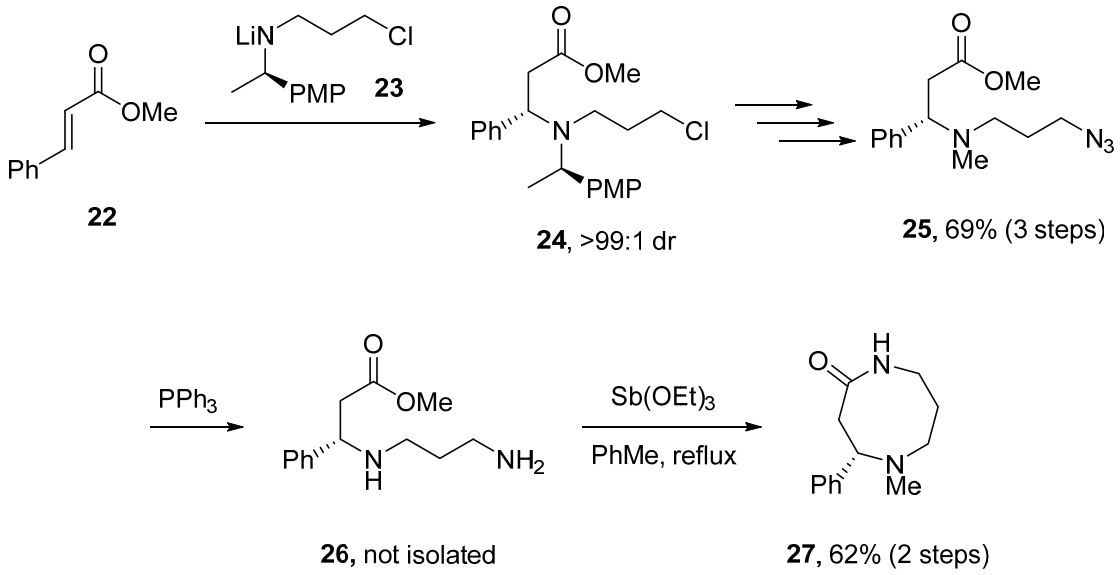
Scheme 4



all proved ineffective in accomplishing the transformation. Despite the risk of forming undesired dimerization products, a metal-templated cyclization using triethylstibenite was attempted and afforded the diazalactams **21** in very good yields.[17] This method has since been utilized in the asymmetric synthesis of the homalium alkaloid (*R*,*R*,*R*)-hoprominol by Hesse *et al*.[21]

The first successful asymmetric synthesis of natural homalium alkaloid (*S*,*S*)-homaline (**1**) was undertaken in 2012 by S.G. Davies *et al*. making use of triethylstibenite to promote the key 8-membered cyclization step (Scheme 5).

Scheme 5



Chiral amino ester **24** was accessed via a highly diastereoselective 1,4-addition of enantiomerically-pure secondary lithium amide **23** to (*E*)-methyl cinnamate which proceeded with >99:1 diastereoselectivity. Sequentially, removal of the *N*-α-methyl-*p*-methoxybenzyl group with trifluoroacetic acid, reductive methylation with paraformaldehyde and sodium cyanoborohydride, and conversion of the primary chloride into a primary azide with sodium azide afforded **25** in 69% yield over three steps. A Staudinger reduction followed by treatment with triethylstibenite at elevated temperatures provided ζ–azalactam **27** in 62% yield over two steps.[22] Also in 2012, the same group reported the first asymmetric synthesis of natural homalium alkaloid (–)-(*R,R*)-hopromine

(**2**) employing the same methodology and starting from chiral amino ester **24**. In exploring alternative routes to the target, it was found that the metal-templated cyclization step fails if the amine nucleophile **26** is modified to be secondary (*N*-allyl) rather than primary. The cyclization also fails if the electrophilic component is a *tert*-butyl ester rather than a methyl ester. These two observations suggest that the antimony-templated cyclization is sterically sensitive.[23]

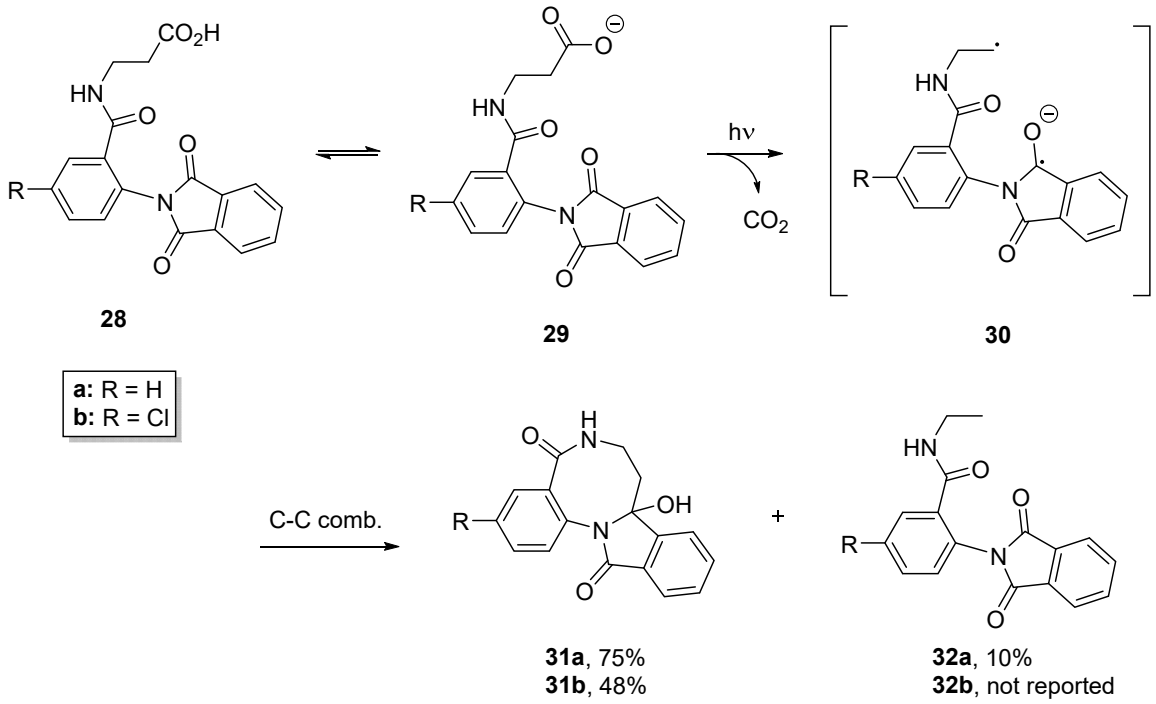
In yet another report from 2012, S.G. Davies *et al*. reported the total syntheses of (–)-(*R,R,R*)-hoprominol (**3**) and (–)-(*4′S,4″R,2‴R*)-hopromalinol (**4**). With modifications to the substituent at the 4-position of α,β-unsaturated ester **22**, the requisite 1,5-diazocanone units required for these syntheses were assembled using the same methodology.[24]

1.5.2 Decarboxylative Photocyclization

Griesbeck and co-workers reported a novel synthetic approach to synthesizing 1,5-benzodiazocines **31** in addition to homologous compounds ranging in ring size from 9–16 members depending on the length of the alkylcarboxy tethered to the benzamide nitrogen (Scheme 6). Decarboxylative intramolecular photocoupling was accomplished in water-acetone (1:1) under a nitrogen atmosphere at 15 °C while irradiated with 300nm light produced from a low pressure phosphor-coated mercury lamp. A decarboxylated anionic biradical **30** was generated and carbon-carbon bond formation between the two radical centers shown was successfully facilitated. The product distribution was that the primary species obtained was the desired benzodiazocine **31** and that the major side product was

that of so-called "simple" carboxylation, forming uncyclized **32**. The chemical yield of this side product is, however, only reported for **32a**.[25]

Scheme 6

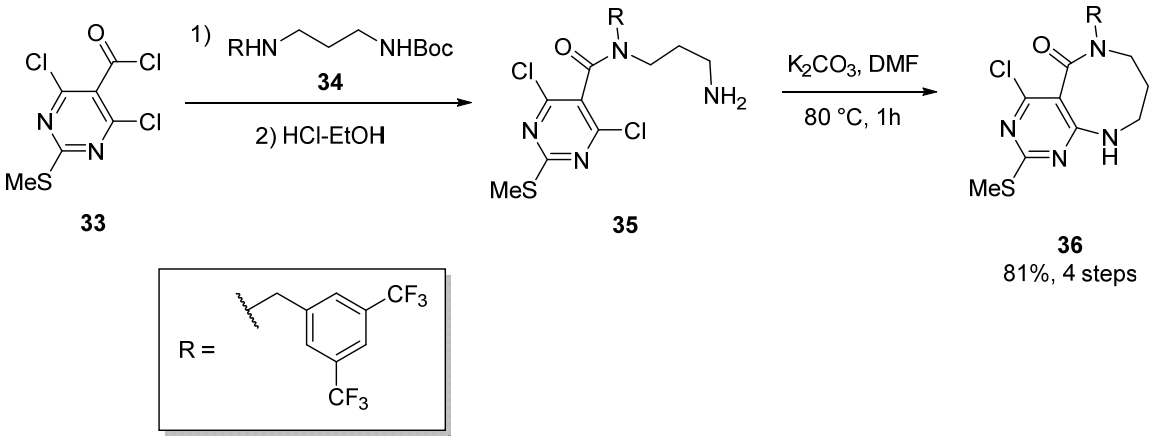


1.5.3 Intramolecular Nucleophilic Aromatic Substitution

In the preparation of potent NK_1 antagonists, Seto and co-workers constructed 1,5-diazacanone **36** which served as a point of divergence from which the targeted bioactive azalactams could be prepared (Scheme 7). Condensation of 4,6-dichloro-2-(methylthio)pyrimidine-5-carbonyl chloride (**33**) with differentially bis-substituted 1,3-diaminopropane **34** followed by removal of the Boc protecting group in acidic ethanol

delivered compound **35**; the immediate precursor to cyclization. Direct 8-membered cyclization was accomplished via intramolecular nucleophilic aromatic

Scheme 7



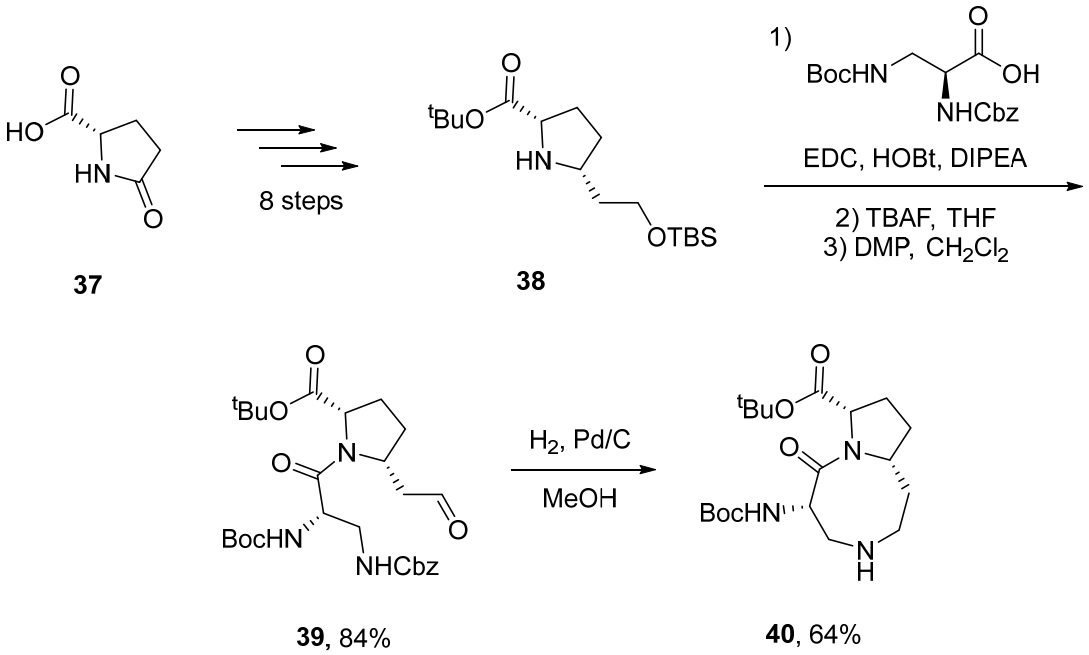
substitution within pyrimidine **35** consisting of the displacement of chloride by the primary amino tether situated ortho to the C_{Ar}-Cl bond via S_NAr afforded bicyclic azalactam **36**. No purification was performed during this sequence until isolation of **36** was performed after which the product was obtained in 81% overall yield.[26]

1.5.4 Intramolecular Reductive Alkylation

In 2006, Wang *et al*. employed synthesized conformationally-constrained reverse-turn mimetic **40** using late-stage direct 8-membered cyclization to access the 1,5-diazocinone moiety (Scheme 8). The 2,5-disubstituted pyrrolidine **38** was obtained via modification of the naturally-occurring amino acid derivative in eight steps. The secondary pyrrolidine was then converted to tertiary amide **39** via peptide coupling with

Z-3-(Boc-amino)-L-alanine followed by deprotection of the primary alcohol and its subsequent oxidation with Dess-Martin periodinane.[27]

Scheme 8



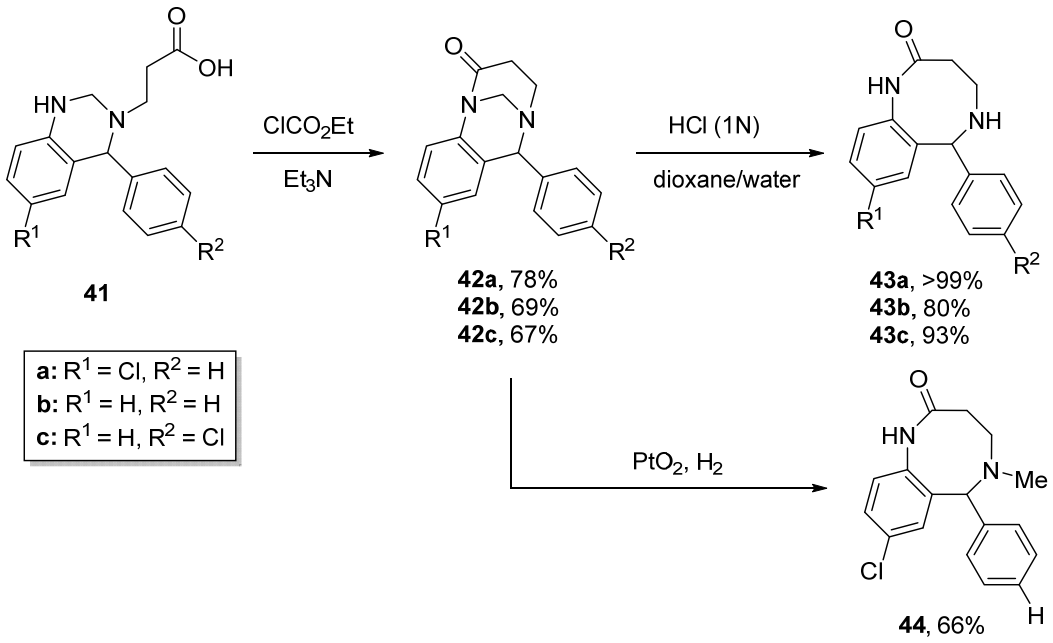
In the key ring-forming tandem sequence, palladium-catalyzed hydrogenative conditions were employed wherein reductive Cbz-deprotection occurred, exposing the primary amino group which was then poised for condensation with the nearby aldehyde group. The corresponding imine was readily reduced under these hydrogenative conditions to furnish the product (**40**) in 64% yield.[27] Over the course of time of 2008 to 2012, Wang *et al*. employed this synthetic method to build up several libraries of potent Smac mimetics for SAR studies.[11,28–30] as well as in the synthesis of effective conformationally-constrained peptidomimetic STAT3 inhibitors.[31] The aforementioned "bivalent" Smac mimetic SM-

1200 (Figure 3, Compound **7**) was synthesized by Wang *et al*. employing this same methodology.[12]

1.6 Fragmentation of 1,5-Bridged 1,5-Diazocin-2-ones

In the first ever reported synthesis of a 1,5-diazocinone in 1969, Denzer and Ott successfully accessed the 8-membered scaffold via twisted amides **42** (Scheme 9). The featured bridged bicyclic species was obtained via the intramolecular acylation of the nitrogen at the 1-position by the β-amino acid tether extending from the nitrogen at the

Scheme 9



5-position of compounds **41**. Subsequent treatment of **42** with dilute hydrochloric acid at room temperature produced benzodiazocines **43** in very good to nearly quantitative yields. In the very same publication, it was reported that the methylene bridge of twisted amide

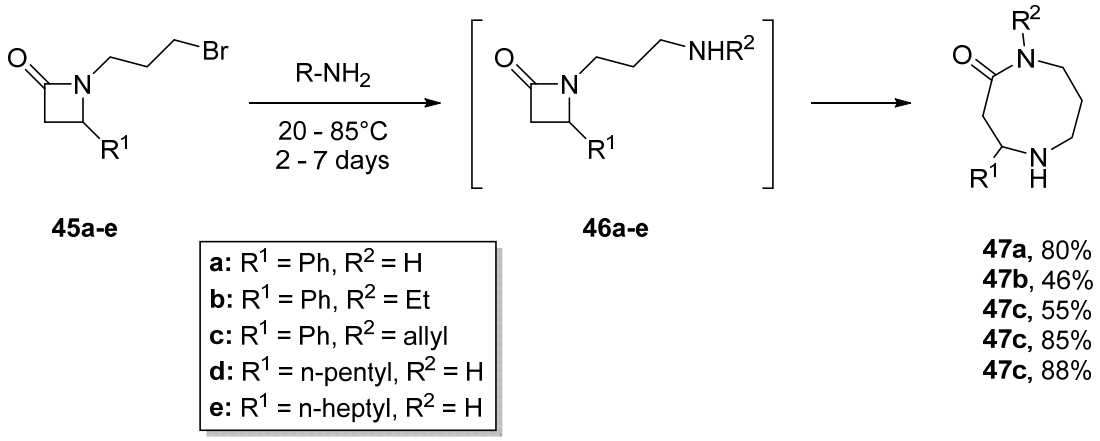
42a could be cleaved under hydrogenative conditions using Adams' catalyst to afford the corresponding 5*N*-methylated analog of **44** (Scheme 9).[1]

1.7 Transamidative Strain-Release Driven Ring-Expansion

The difficulty of the direct cyclization of 1,5-diazocin-2-one ring systems lead to the use of alternative forms of activation to gain access to the ring system. Rather than promoting the cyclization via the activation of one of the functionalities with a chemical agent during the ring forming step, strain energy release has also been employed.

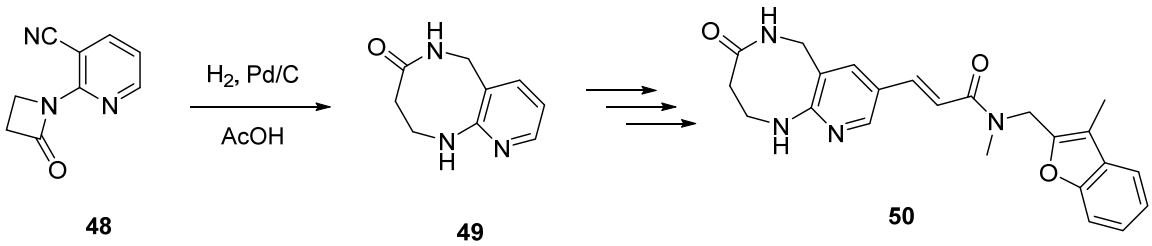
Crombie and Jones *et al*. developed a strain release driven reaction to form saturated 1,5-diazacan-2-ones **47** as well as their 7- and 9-membered homologues (Scheme 11). The treatment of brominated azetidines **45** with a primary amine in a sealed reaction tube for 2–7 days facilitated nucleophilic substitution to generate *N*-aminoalkylazetidinone intermediates **46**. The strain energy of the geometrically-constrained 4-membered azacycle provided the thermodynamic driving force for intramolecular transamidative ring-expansion to afford products **47**. For yields shown in Scheme 10, the reaction was carried out without isolation of the *N*-aminoalkylazetidinone intermediates **46**. However, by stopping the reaction during its normal course, the isolation and structure elucidation of intermediates **46a** and **46b** was possible – evidence that the reaction proceeds via an intramolecular transamidation.[32] This method has since been used in the synthesis of natural homalium alkaloids (±)-dihydroperiphylline,[33] racemic as well as (–)-homaline,[34] (±)-hopromine, (±)-hoprominol, (±)-hopromalinol,[35] as well as unnatural analogs[8] of the homalium group of alkaloids.

Scheme 10



Pauls and Ramnauth *et al*. employed an intramolecular transamidative strategy in the synthesis of FabI inhibitor candidate **50** (Scheme 11). Upon hydrogenation of nitrile **48** with hydrogen gas using palladium on carbon as the catalyst in the presence of acetic acid, spontaneous transamidation occurred forming intermediate **49** in the synthesis of oxindole-containing species **50** – although no yield was reported.[36]

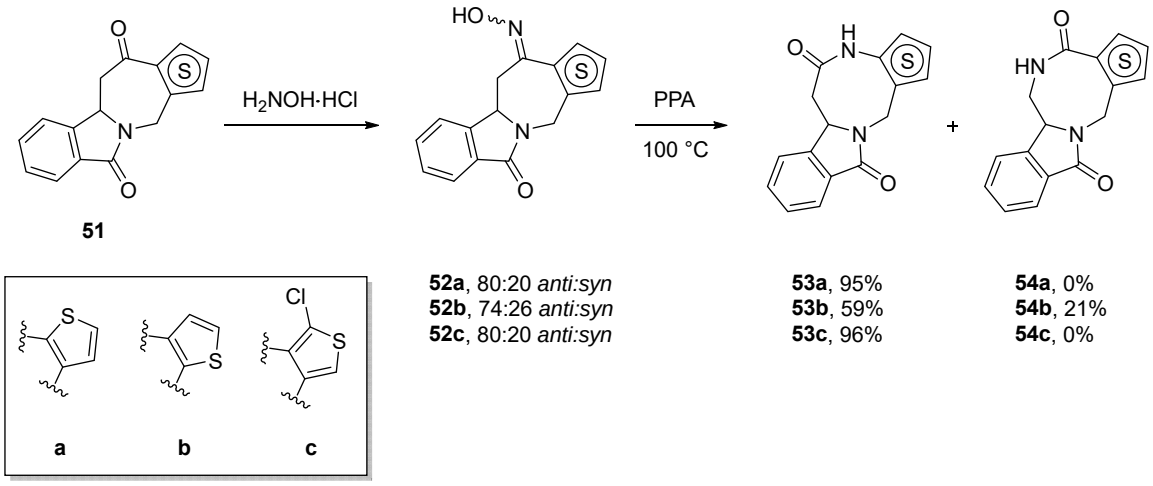
Scheme 11



1.8 Beckmann Rearrangement of 4-Azepinone Oximes

Fused tetracyclic isoindolodiazocinones **53** were found by Decroix *et al*. to be accessible from 4-azepinones **51** via the Beckmann rearrangement (Scheme 12). Azepinones **51** were converted into the corresponding oximes **52** via the treatment with hydroxylamine hydrochloride and sodium acetate in a refluxing ethanol-water solution.

Scheme 12



Oximination provided a mixture of configurational isomers with the *anti* isomer (i.e. with the hydroxyl group of the oxime further rather than nearer to the thiophene ring) dominating in every case. After only very coarse purification, the mixtures were heated in polyphosphoric acid for 45 minutes to provide the desired diazocines **53**. It is worth noticing that in the cases of **52a** and **52c**, both the *syn* and *anti* oximes were converted to the desired 1,5-diazocenes **53a** and **53c** in excellent yields with no observed 1,4-diazocine **54**. On the other hand, the mixture of *anti* and *syn* oximes **52b** led to the 1,5-diazocine and

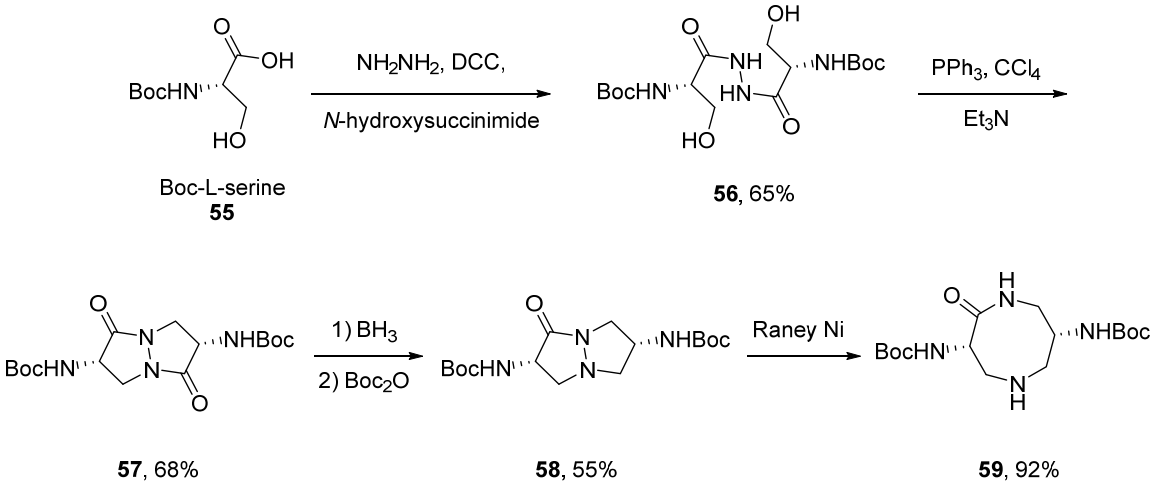
the 1,4-diazocine, respectively. This suggests that, in the cases of **53a,b**, the *syn* oximes undergo isomerization into the *anti* oximes prior to the rearrangement. This is not the case for the oxime mixture **53b**.[37]

1.9 Reductive N-N Bond Scission

One strategy for accessing the 1,5-diazocinone moiety is to first construct a 1,5-diazabicyclo[3.3.0]octan-2-one which is poised for reductive cleavage of the N-N double bond; effectively destroying the 1,5-fusion to unveil the 8-membered moiety. This approach offers the advantage of the relative ease with which 5-membered rings can be cyclized versus cyclizations to afford 8-membered cycles.[38]

The first such reported method was toward the end of synthesizing chiral polyamines designed to bind to the vanadate anion (VO_4^{3-}) to form functional mimics of the marine algae vanadium haloperoxidases (Scheme 13).[38]

Scheme 13



Boc-L-serine **55**

56, 65%

57, 68%

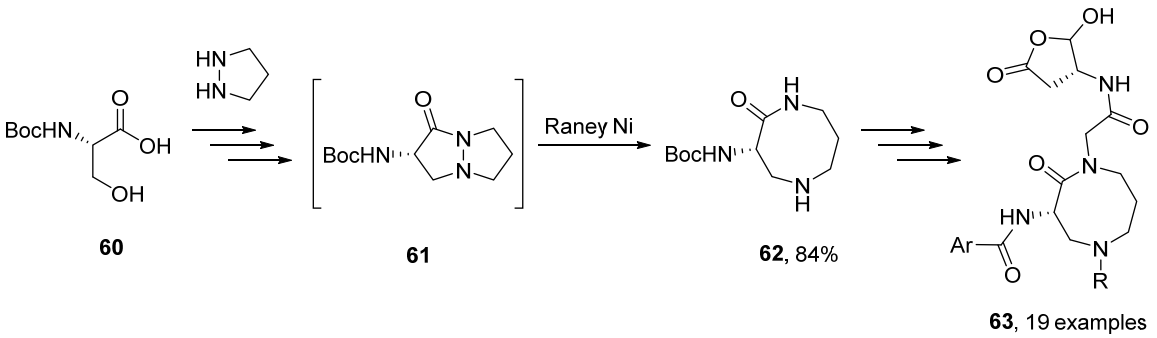
58, 55%

59, 92%

The coupling of two *N*-Boc-protected serine units **55** to a single hydrazine unit yields diacylhydrazide **56** in moderate yield (65%). Conversion of the alkyl hydroxyl groups to chlorine *in situ* and subsequent intramolecular alkylation was accomplished via classical Appel reaction conditions to give the chiral 1,5-diazabicyclooctanone **57**. An unprecedented selective monoreduction employing BH_3·THF followed providing the key intermediate **58** in moderate yield (55%). The Boc protecting group proved to be less than completely stable to the reaction conditions for this reduction. The addition of Boc anhydride to the reaction mixture after quenching borane was essential to "reprotect" any naked amino groups. The facile cleavage of the nitrogen-nitrogen bond was accomplished with Raney nickel providing diazocine **59** in excellent yield.[38]

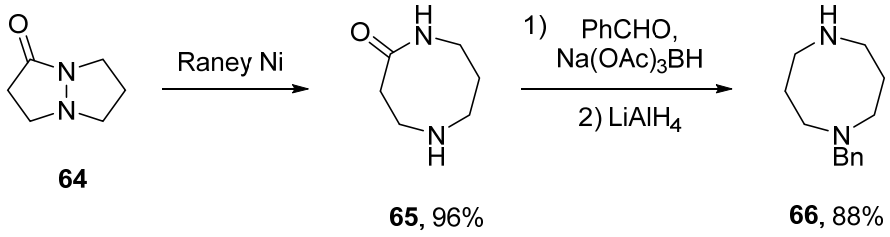
Oppong *et al*. employed this method in an effort to synthesize a small library of potential ICE inhibitors for SAR studies (Scheme 14). Also starting from Boc-L-serine, EDC coupling with pyrazolidine followed by intramolecular Mitsunobu reaction produced intermediate **61**. As with the synthesis of compound **59**, treatment with Raney nickel was effective in cleaving the central N-N bond and furnishing diazocanone **62**; the basis scaffold from which targets **63** were assembled. No chemical yields of ICE inhibitor candidates **63** were reported.[9]

Scheme 14



The first synthesis of unsubstituted 1,5-diazocan-2-one (**65**) was realized when prepared as an intermediate en route to simple mono-protected 1,5-diazacyclooctane **66** (Scheme 15). The cleavage of the N-N bond was accomplished in high yield using Raney nickel. The successful synthesis of **66** established a novel route to differentially-protected 1,5-diazacyclooctanes via the 1,5-diazocan-2-one moiety.[39]

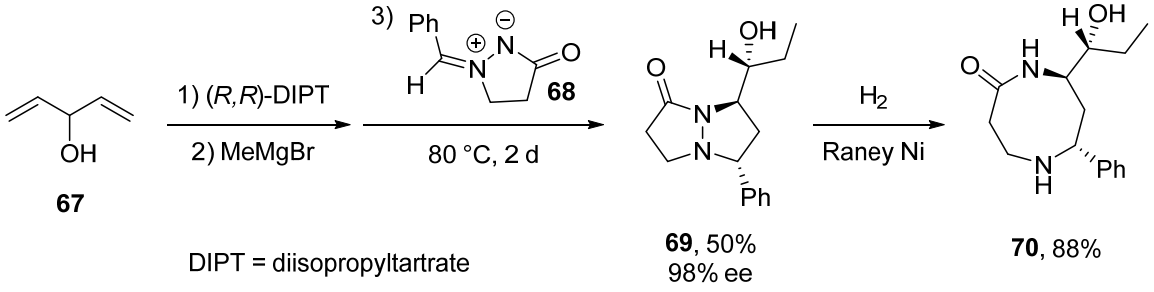
Scheme 15



Ukaji *et al*. reported on the desymmetrization of 1,4-pentadien-3-ol (**67**) in the synthesis of optically active 1,5-diazabicyclooctanones via asymmetric 1,3-dipolar cycloaddition; the products of which could then be converted to the corresponding diazocanones (e.g. **70**) via reductive cleavage of the N-N bond (Scheme 16). This proceeds via a magnesium-mediated multinucleating chiral reaction wherein pentadienol **67** and

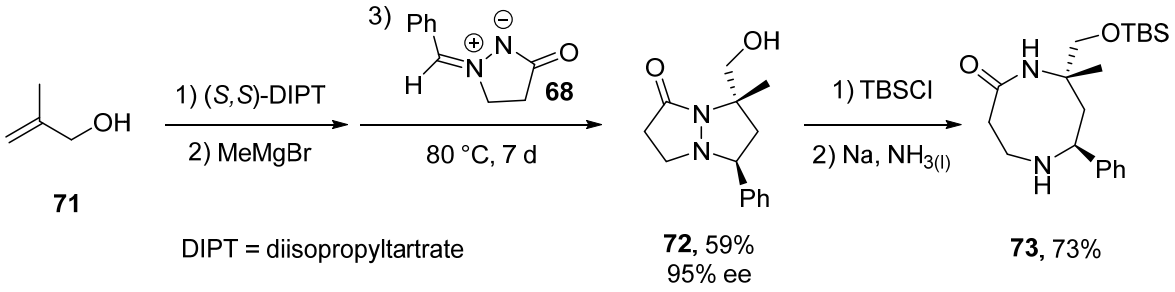
azomethine imines **68**, and (*R,R*)-diisopropyltartrate – upon treatment with 3 equivalents of methylmagnesium bromide – form a coordination complex in which the chiral tartrate serves as a highly effective chiral auxiliary. The cycloaddition afforded the product **69** in modest yield and 98% enantiomeric excess. Reductive scission of the N-N bond with Raney nickel afforded diazocanone **70** – containing three new stereogenic centers – in 88% (44% overall) yield and with high optical purity.[40]

Scheme 16



In a subsequent 2017 report, Ukaji *et al*. applied their previously-developed conditions to alcohol substrate **71** which provided optically active 1,5-diazabicyclooctanone **72** in moderate yield and high enantioselectivity (Scheme 18). Having made use of (*S,S*)-DIPT, product **72** possessed the opposite sense of chirality than that of product **69** from the initial 2014 report described above (Scheme 16). Electing to cleave the N-N under dissolved alkali metal conditions with sodium in liquid ammonia after silyl protection with *tert*-butyldimethylsilyl chloride, diazocanone **73** was furnished in good yield.[41]

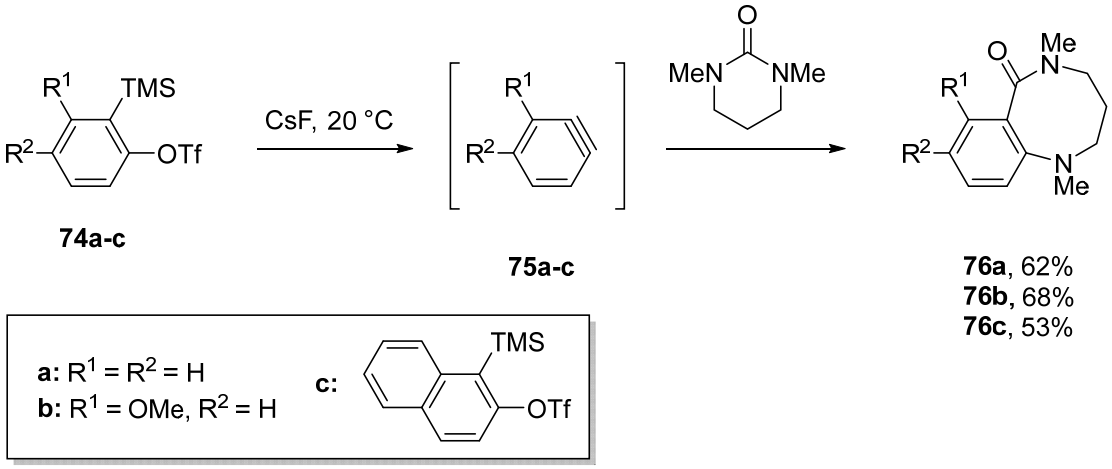
Scheme 17



1.10 Addition of Ureas to Arynes

In 2002, T. Hiyama *et al*. reported the novel, regioselective insertion of arynes into the more common N-CO bond of ureas (Scheme 18). Aryne equivalents **74** were subjected to fluoride in order to induce 1,2-elimination to form the reactive intermediates **75**. Before the early 2000's, the addition of a nucleophile single-bonded to an electrophile (with the exception of a proton as the electrophile) across the aryne triple bond was generally possible only in the case of species containing specially-activated Nu-E bonds (e.g. Te-Te, S-S, C-Si, and C-Sn).

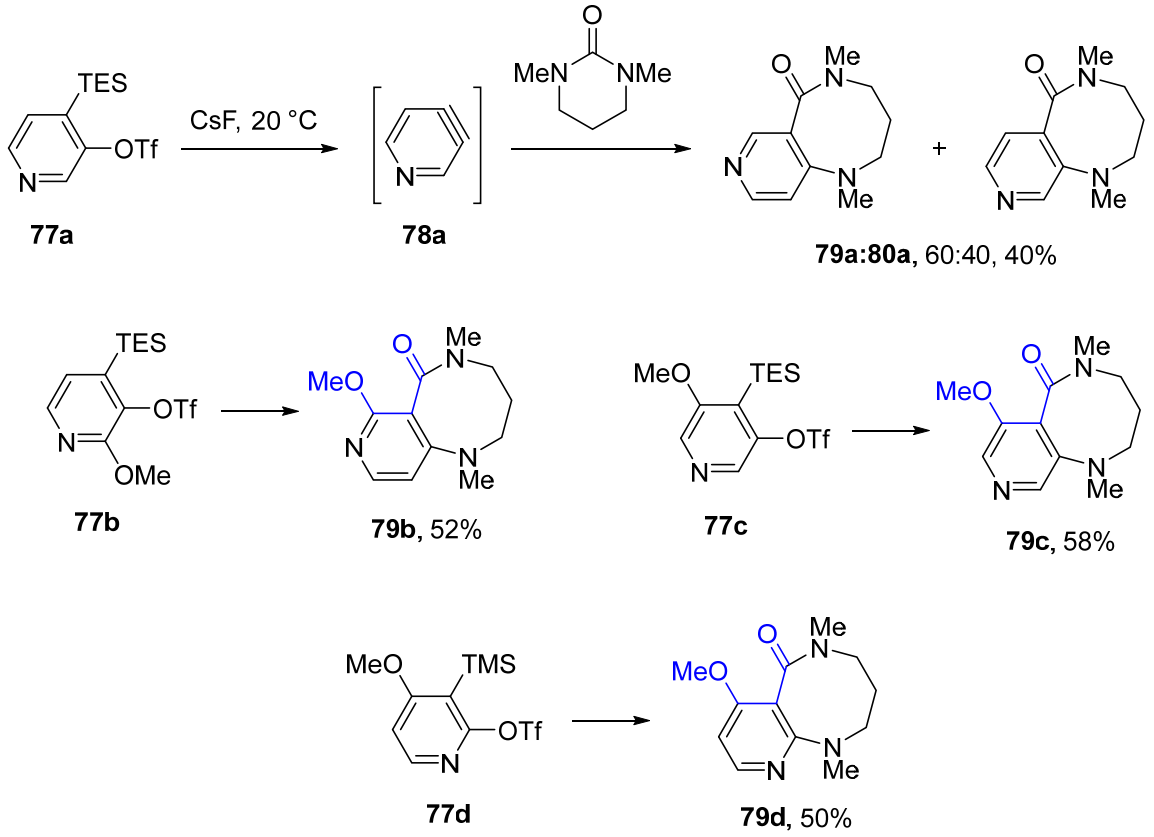
Scheme 18



Treatment with N,N'-dimethylpropyleneurea (DMPU) provided benzodiazocines **76** in moderate yield. Compounds **76** were formed with perfect regioselectivity, with the amide function placed at the more sterically congested site. The remarkably mild conditions, relatively low cost of reagents, and low step-count make this an attractive method for accessing the 1,5-benzodiazocine core.[42]

Pyridines were employed as aryne (i.e. pyridyne) precursors by Sato *et al*. in 2013 in the synthesis of bicyclic pyridines analogous to benzodiazocines **37** (Scheme 19). The methodology is essentially the same, using cesium fluoride at room temperature to generate pyridynes from silyl-protected pyridine triflates **77** to react subsequently with *N,N'*-dimethylpropyleneurea (DMPU) affording fused bicyclic diazocinones **79** in moderate yield. Reaction of pyridine **77a** with DMPU was only slightly regioselective, providing a distribution of products **79a** and **80a** in a 60:40 ratio. Reactions of the isomeric methoxy-substituted pyridines **77b-c** each afforded a single regioisomer in moderate yield.

Scheme 19

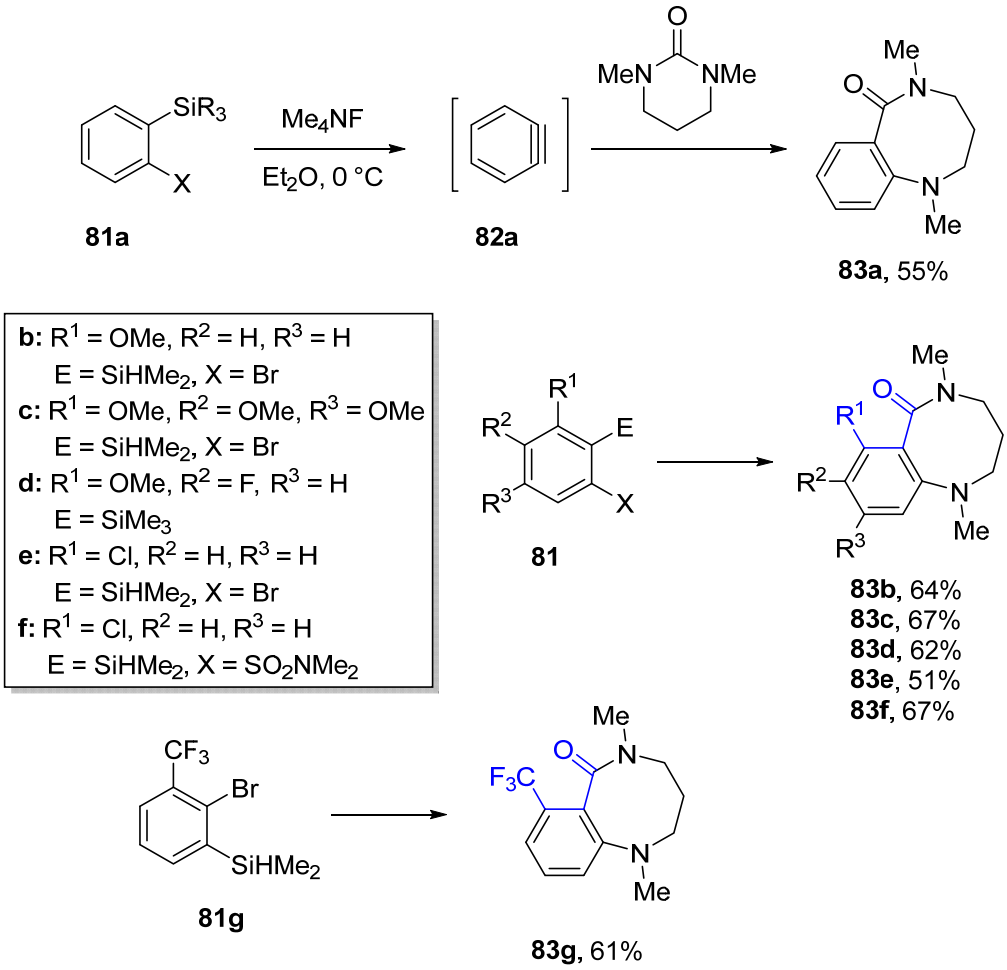


The incorporation of the methoxy group imparted to the reaction a strong regiochemical preference for a 1,3-relationship between the methoxy-bearing carbon and the carbonyl carbon. I.e. a strong preference exists for the diazocinone product with the least steric congestion near the aniline nitrogen. This is in keeping with the rational that the first step in the cyclization sequence is the nucleophilic attack of the urea nitrogen on an aryne carbon. This attack occurs at the least sterically hindered position.[43]

In a 2015 report by Daugulis *et al*., a variation on aryne precursors for the formation of 1,5-diazocin-2-ones was presented. The traditional triflate leaving group was replaced

with bromide – and in one example, a sulfamate – while cesium fluoride was replaced with tetramethylammonium fluoride.

Scheme 20



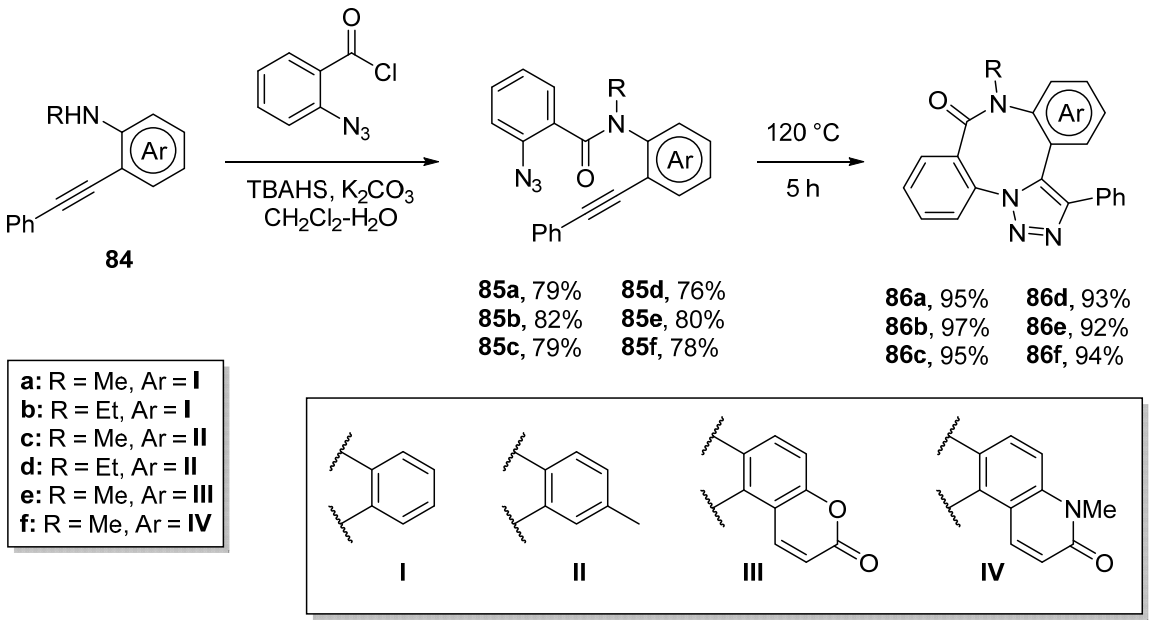
From precursors **81**, arynes of type **82** were generated *in situ* and the subsequent reaction with DMPU to afford provided benzodiazocinones in yields comparable to earlier reported reactions employing triflates (Scheme 20). Also in keeping with previous findings, the reaction exhibits a strong regiochemical preference for products with the least steric congestion near the aniline nitrogen.[44]

1.11 Intramolecular Azide-Alkyne Huisgen Cycloaddition

The year 2010 saw two independent reports of the unprecedented use of Huisgen dipolar cycloaddition to furnish 1,2,3-triazole-fused benzo[1,5]-diazocinones – a unique diazocinone scaffold; the likes of which had been hitherto absent from the chemical literature.

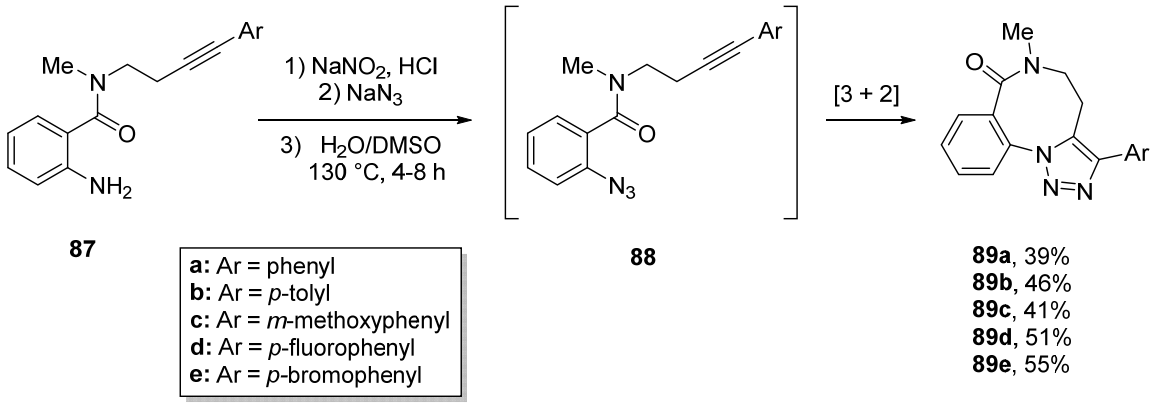
In an unprecedented route to molecules possessing the 1,5-diazocin-5-one moiety, Majumdar *et al*. reported the synthesis of 1,2,3-triazole-fused dibenzo[1,5]-diazocinones **86** via an intramolecular Huisgen [2+3] cycloaddition (Scheme 21). Cycloaddition precursors **85** were prepared in good yields via acylation of 2-(phenylethynyl)anilines **84** with 2-azidobenzoyl chloride. Over the course of five hours, the subsequent cyclization proceeded smoothly for all substrates **76** at 120 °C to furnish the products **86** in excellent isolated yields. Variation of R and/or Ar groups did not majorly affect the yields of azides **85** nor their corresponding cyclized products (**86**).[45]

Scheme 21



In a separate and independent instance in 2010, Chowdhury *et al*. reported the synthesis of a collection of similar 1,2,3-triazole-fused benzo[1,5]-diazocinones **89** (Scheme 22). The 1,2-substituted benzene rings **87** were prepared as anilines (rather than as azides **85**). In a single reaction vessel, diazotization of anilines **87** was facilitated by nitrous acid and, upon the addition of sodium azide, was subsequently converted into organic azide intermediate **88**. Cyclization at elevated temperatures occurred to furnish diazocines **89** in a three step, one pot process.[46]

Scheme 22



87

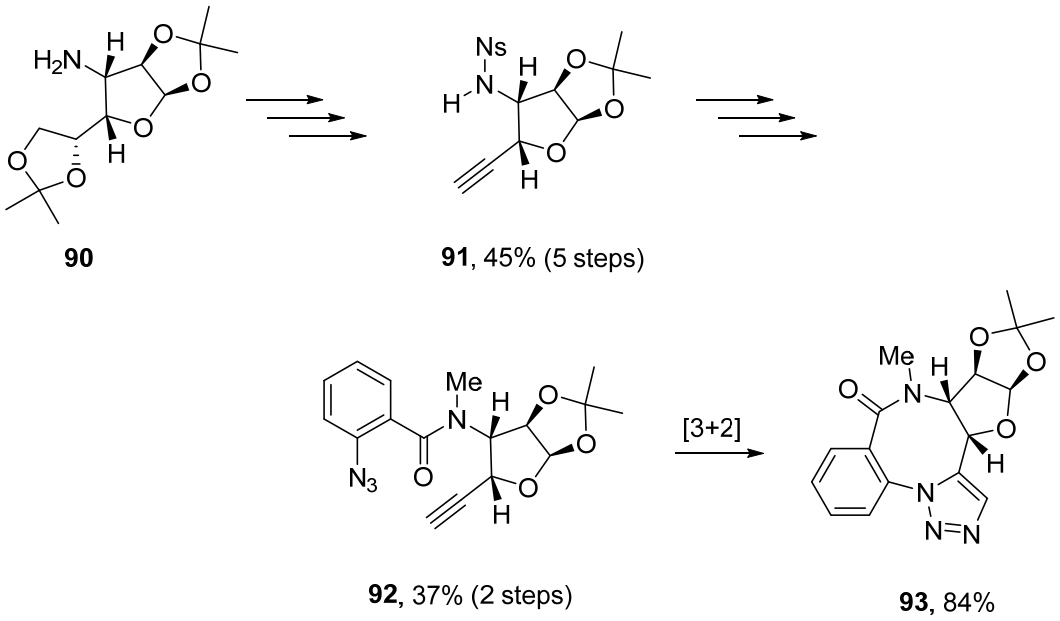
a: Ar = phenyl
b: Ar = *p*-tolyl
c: Ar = *m*-methoxyphenyl
d: Ar = *p*-fluorophenyl
e: Ar = *p*-bromophenyl

88

89a, 39%
89b, 46%
89c, 41%
89d, 51%
89e, 55%

With interest in 1,2,3-triazole-fused 8-membered heterocycles as bioactive molecules growing, in 2012 Chattopadhyay *et al*. directed their efforts toward the synthesis of chiral non-racemic molecules of these types, including the first example of a chiral 1,2,3-triazole-fused benzo[1,5]-diazocinone (Scheme 23). Starting material α-D-glucofuranoside **90** was, in sequence, *N*-nosyl-protected with nosyl chloride and *N*-methylated with methyl iodide. Selective conversion of the non-fused vicinal diol was accomplished with acetic acid at room temperature. The diol treated with sodium periodate and then Bestmann's reagent to afford terminal alkyne **91** (45%, 5 steps) via Seyferth-Gilbert homologation. Removal of the nosyl protecting group with thiophenol followed by acylation of the amine nitrogen with 2-azidobenzoyl chloride provided cycloaddition precursor **92** (37%, 2 steps).

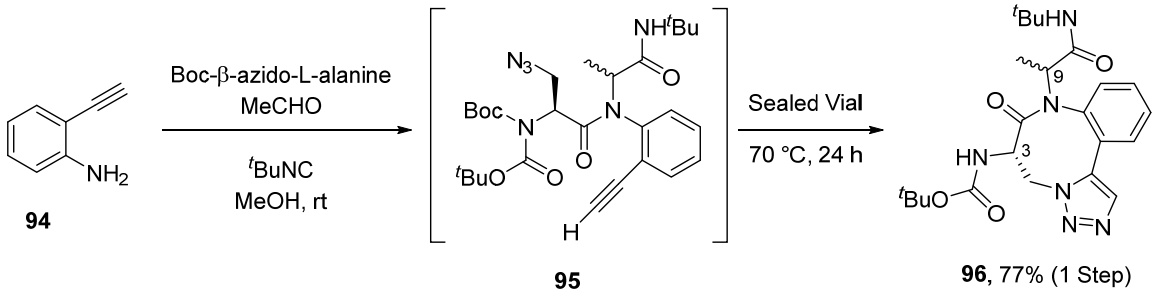
Scheme 23



Upon heating at 120 °C for 2h in dry dimethylformamide, intramolecular azide-alkyne Huisgen cycloaddition occurred providing chiral 1,2,3-triazole-fused furobenzodiazocinone **93** in good yield.[47]

In 2016, Ballet and Jida *et al*. demonstrated an efficient route to conformationally-constrained tricyclic 1,2,3-triazole-fused benzo[1,5]-diazocinones via a tandem Ugi-Huisgen sequence (Scheme 24). The reaction of 2-ethynylaniline (**94**) with Boc-β-azido-L-alanine, acetaldehyde, and *tert*-butyl isocyanide in methanol at room temperature afforded the Ugi product **95** as the direct precursor to 1,3-dipolar Huisgen cycloaddition which was facilitated by heating at 70 °C for 24 hours. The chiral 1,2,3-triazole-fused benzo[1,5]-diazocinone **96** was obtained in 77% yield. Despite stereoretention at C(3), stereocontrol at C(9) was not achieved.[48]

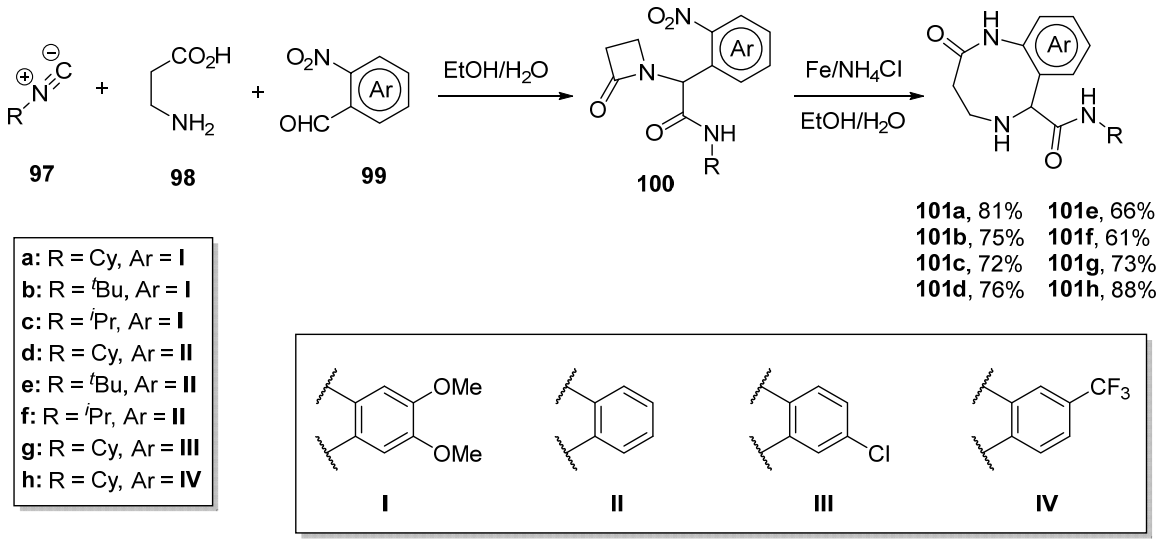
Scheme 24



1.12 Ugi Four-Center Three-Component and Subsequent Reductive Cyclization

A tandem one-pot, three component Ugi reaction and subsequent reductive cyclization was developed by Chattopadhyay in 2012 for the synthesis of 1,5-benzodiazocine-2-ones **101** (Scheme 25). β-Lactams **100** were formed at room temperature from isocyanates **97**, β-alanine (**98**), and 2-nitrobenzaldehydes **99**.

Scheme 25

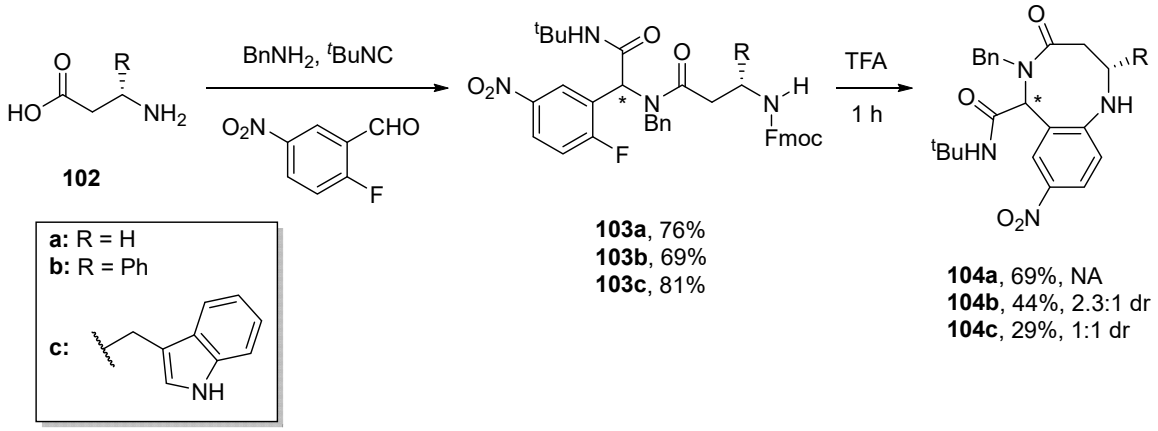


Poor yields were obtained when *o*-tolyl and 2-naphthyl isocyanates were used leading the authors to focus on aliphatic isocyanates. Several reagent systems, including zinc metal and also tin in acetic acid, successfully reduced the nitro group. However, in these cases, the desired subsequent cyclization failed to occur. With its mild acidity and high functional group tolerance, Fe/NH_4Cl was screened as a reducing agent and was found to allow for successful cyclization post-reduction. The placement of electron withdrawing groups on the aryl ring was found to increase the rate of the reaction significantly. Furthermore, higher yields were obtained when the isocyanate bore a cyclohexyl substituent as opposed to *iso*-propyl or *tert*-butyl substituents. It is reasoned that this is likely due to the cyclohexyl group being sterically smaller than the others. Performed in a one-pot, two-step fashion, diazocines **101** were provided with yields of 61-88%.[49]

1.13 Ugi Four-Component Reaction and Subsequent Intramolecular S_NAr

Biron *et al*. reported in 2017 the two-step sequence of Ugi four-component reaction followed by nucleophilic aromatic substitution initiated by Fmoc-deprotection to afford bicyclic 1,5-benzodiazocin-2-ones **104** (Scheme 26). β-amino acids **102** reacted in a Ugi reaction with benzylamine, *tert*-butyl isocyanide, and 2-fluoro-5-nitro-benzaldehyde in methanol:dichloromethane (2:1) for 72 hours at ambient temperature to afford the expected Ugi products **103** in good yields.

Scheme 26

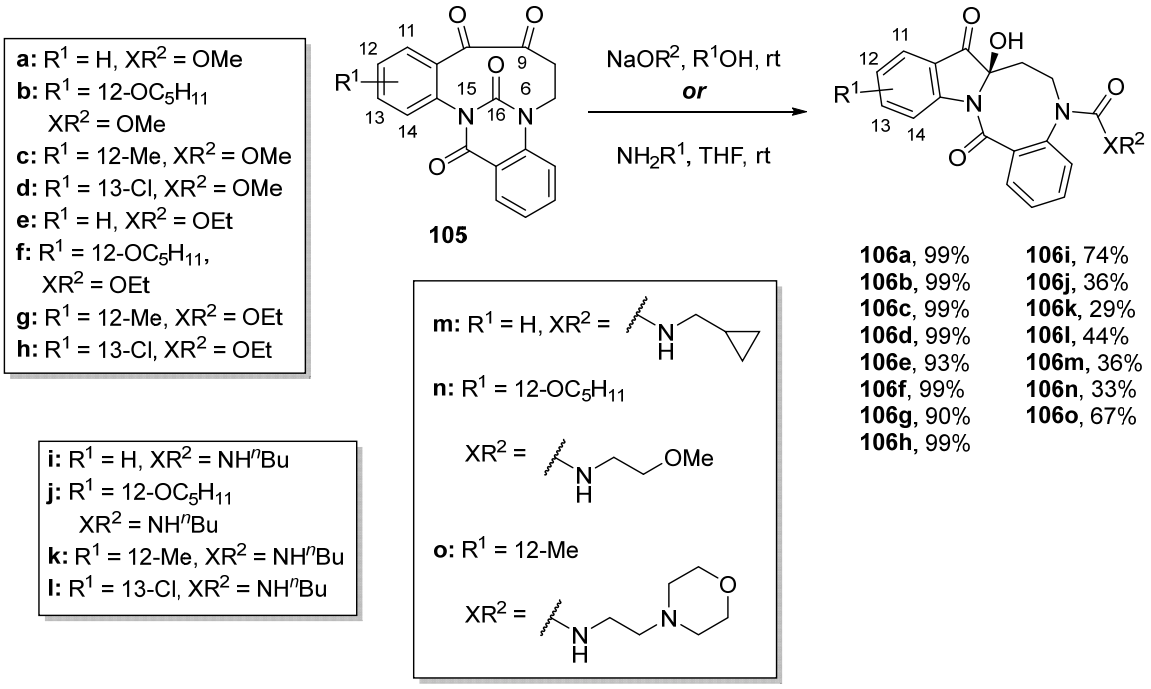


Upon removal of the Fmoc protecting group with trifluoroacetic acid, nucleophilic displacement of the arene fluorine substituent occurred providing azalactams **104** with yields ranging from poor to moderate. The bicyclic products containing multiple stereogenic centers were obtained as mixtures of diastereomers. The diastereomeric ratios in the cases employing β-amino acids **102b** and **102c**, were 2.3:1 and 1:1, repectively.[50]

1.14 Nucleophile-Induced Rearrangement of 9-Membered Ureas

A novel method for accessing chiral, tetracyclic diazocinones **106** was reported by Jones and Westwood *et al*. in 2016 (Scheme 27). The method involves a rearrangement initiated by a nucleophilic attack of an alkoxide (or amine) on the urea carbonyl carbon

Scheme 27



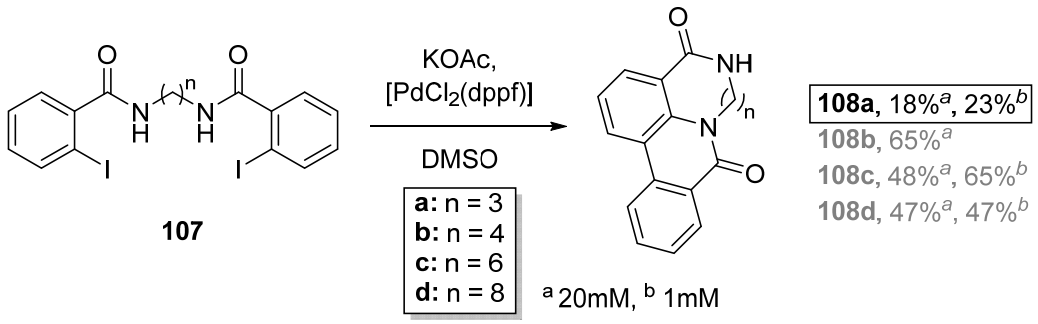
C(16) of substrates **105**. It is proposed that the nucleophilic attack causes subsequent ring-opening via the cleavage of the C(16)-N(15) bond, forming an 11-membered macrocyclic intermediate. It is proposed that subsequent ring-closure via nucleophilic attack of N(15) on carbonyl C(9) takes place to afford the 5,8-fused system (i.e. compounds **106**) from the starting [8.3.1]-bridged ring system of starting materials **105**. Reactions with alkoxides proceeded rapidly (i.e. complete within 10 minutes) and with excellent yields (90-99%) while reactions employing amines as nucleophiles proceeded less rapidly (completion within 3 hours) and with much poorer yields (33–74%).[51]

1.15 Metal-Catalyzed Tandem Processes

1.15.1 Palladium-catalyzed Domino Synthesis of Tetracyclic Diazocines

In 2003, Zhu *et al*. disclosed a novel palladium-catalyzed domino process for the conversion of simple linear diamides **107** into the complex fused tetracycles **108** in a single reaction vessel (Scheme 28). The transformation consists formally of the formation of one C_{Ar}-C_{Ar} bond and one C_{Ar}-N bond accompanied by the instantiation of both a 6-membered

Scheme 28

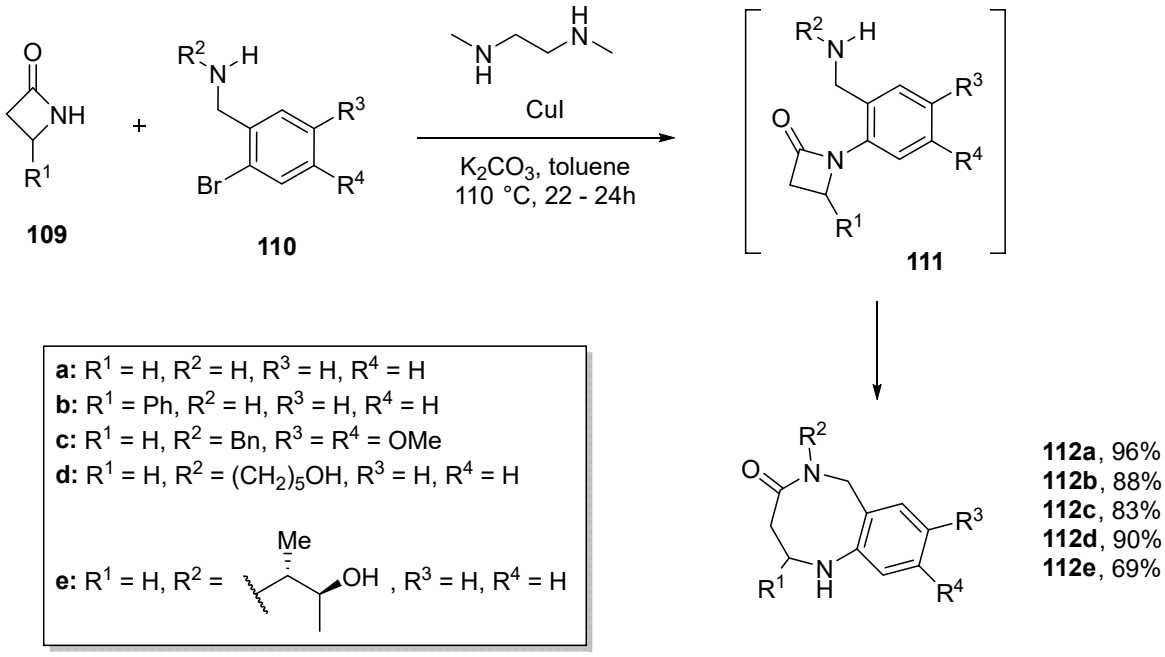


and an (n + 5)-membered ring. It is speculated that the sequence is that of an intramolecular Buchwald-Hartwig amination followed by C-H activation and subsequent aryl-aryl bond formation. Although the reaction provided modest and very consistent yields for the tetracyclic fused lactams **108b, 108c**, and **108d** – corresponding to 9-, 11-, and 13-membered azalactams, respectively – azalactam **108a** (i.e. the product containing the relevant 1,5-diazocinone core) was obtained in much lower yield (18%).[52] In a follow-up publication, further optimization of this reaction was attempted. It was found that diluting the reaction to 1 mM – versus the initially-reported 20 mM – improved yields in some cases although only by a small amount in the case of the 1,5-diazocinone.[53]

1.15.2 Copper-catalyzed Tandem Synthesis of Bicyclic Diazocines

A one-pot tandem sequence to afford substituted benzodiazocines **112** was developed by Buchwald *et al*. and reported in 2004 (Scheme 29). The sequence is that of an Ullman-type coupling of unsubstituted and 4-substituted azetidinones **109** with bromobenzylamines **110** followed by intramolecular transamidation of intermediates **111** to provide 1,5-benzodiazocines **54** in good to excellent yields. Incorporation of a phenyl

Scheme 29

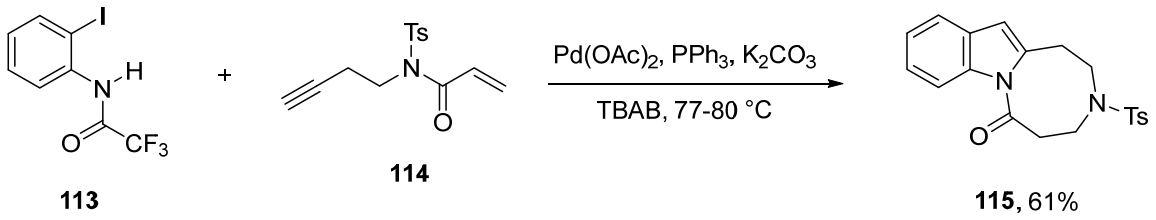


group at the 4-position of the β-lactam was well tolerated as were *N*-benzylated and *N*-alkylated bromobenzylamines. Yield suffered a significant amount with the use of a sterically-congested bromobenzylamine (**110e**).[54]

1.15.3 Palladium-catalyzed Tandem Synthesis of Indole-Fused Tricyclic Diazocines

Q. Wang *et al*. reported in 2015 the development of a route to unique fused tricyclic diazocines (Scheme 30). Under moderate conditions, trifluoroacetyl-protected 2-iodoaniline **113** undergoes a single-pot tandem reaction with terminal acetylene **114** to form 1,2-indole-fused diazocine **115** in moderate yield (61%).

Scheme 30



113 **114** **115**, 61%

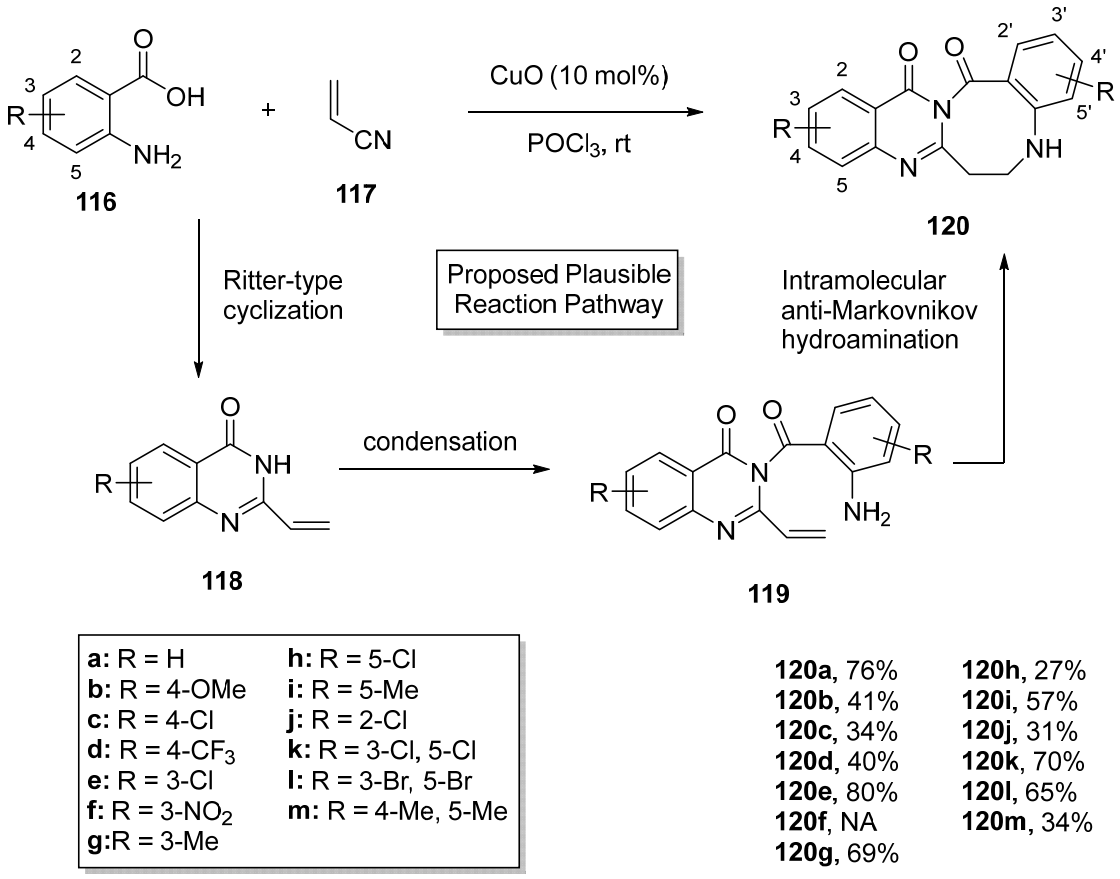
The authors reason that the reaction begins with the Sonogashira coupling of the two components, and proposed five different pathways are proposed the subsequent steps in the mechanistic sequence. Palladium acetate and triphenylphosphine form the catalyst while potassium carbonate serves as the base. The phase transfer catalyst tetrabutylammonium bromide (TBAB) was found to be essential to the proceeding of the reaction.[55]

1.15.4 Copper-Catalyzed Ritter-Condensation-Hydroamination Process

In 2017, Abe *et al*. reported the first synthesis of quinazoline-fused diazocines in a copper-catalyzed tandem process (Scheme 31). Aminobenzoic acids **116** reacted with

acrylonitrile (**117**) in the presence of copper(II) oxide and phosphorus oxychloride at room temperature to afford quinazoline-fused tetracyclic diazocines **120** in mostly modest yields.

Scheme 31



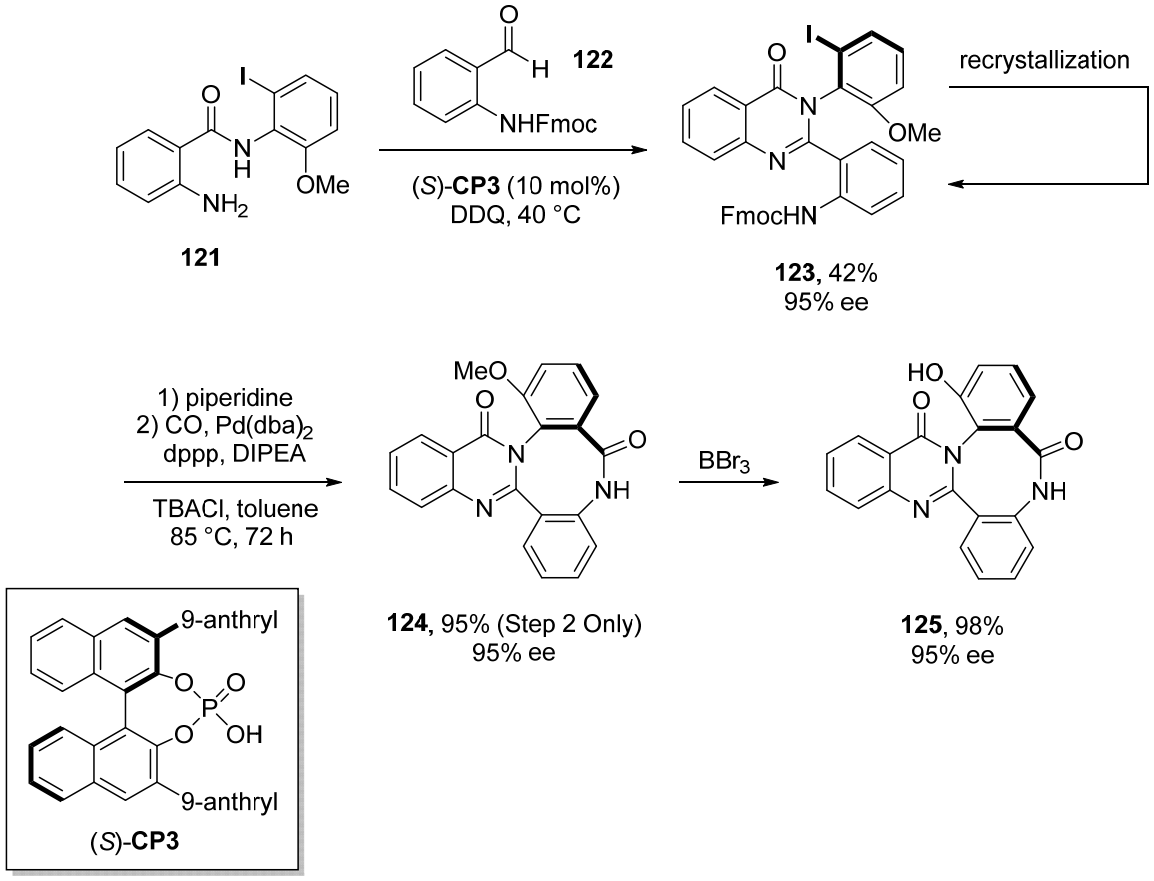
The authors propose a reaction pathway in which benzoic acid **116** reacts with acrylonitrile in a Ritter-type cyclization to afford intermediate **118** which then condenses with another equivalent of aminobenzoic acid **116** forming adduct **119** which undergoes intramolecular hydroamination to furnish the anti-Markovnikov product **120**. Substitution at the aryl ring of benzoic acids **116** has the general effect of lowering the chemical yield of the product. Strong general trends based on steric and/or electronic effects were not observed. With the

introduction of a nitro group into the aryl ring, the desired product was not obtained and a complex mixture of products instead resulted.[56]

1.16 Palladium-Catalyzed Carbonylative Cross-Coupling

In a report by Tan *et al*. in 2017, the asymmetric total synthesis of natural arylquinazolinone-fused diazocine eupolyphagin (**125**) via axially chiral arylquinazolinone **123** was described (Scheme 32). In the asymmetry-inducing step, phosphoric acid **CP3** was employed as a chiral Brønsted acid catalyst in condensation of benzaldehyde **122** with aminobenzamide **121** with subsequent dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the axially-chiral arylquinazolinone **123** in an initial yield of 95%, but exhibiting an enantiomeric excess of only 58%. Recrystallization from dichloromethane/ethyl acetate afforded the material with an improved enantiomeric excess of 95% with a diminished yield of 44%. The high yielding (91%) removal of the Fmoc protecting group with piperidine was accomplished with no effect on optical purity to afford the immediate precursor to the formation of the diazocine core (**124**). Employing bis(dibenzylideneacetone)palladium(0) and dppp as the catalyst, compound **124** was treated with carbon monoxide in the presence of tetrabutylammonium chloride to effect a carbonylative Buchwald-Hartwig-type reaction,

Scheme 32



furnishing pentacyclic 1,5-diazocinone **124** in 95% yield and full retention of enantiomeric purity. Conversion of the methoxy group with boron tribromide delivered the natural product eupolyphagin (**125**) in excellent yield and high enantiopurity (95%).[57]

1.17 Conclusion

Over the course of more than 50 years, many effective methods by which to synthesize 1,5-diazocin-2-ones have been developed which have produced a diverse set of members of the class. Many compounds possessing the unique structural core exhibit interesting biological activities warranting the further exploration of this still vastly unprobed chemical space.

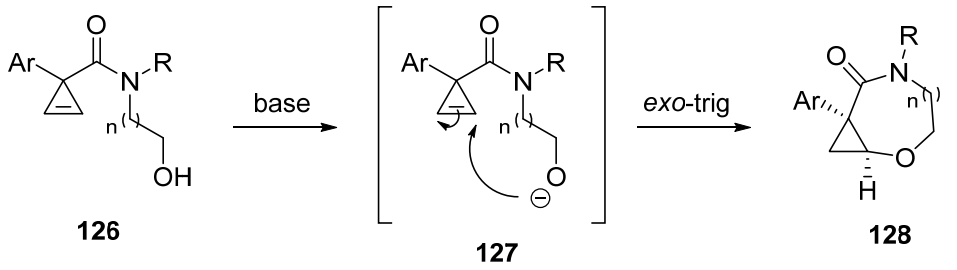
Chapter 2. The Development of a Modular Synthetic Route to Synthetic Precursors to Cyclopropane-Fused 1,5-Diazocin-2-ones

2.1 Introduction

As described in the previous chapter, access to compounds containing the 1,5-diazocin-2-one scaffold is highly desirable due their potential as important pharmaceuticals, yet the methodological avenues and functional group variability remain underexplored. Thus, new synthetic methods for accessing these species – as well as in gaining access to novel members of the class – are in demand. The diversity of available methods for their synthesis (discussed in Chapter 1) include the expansion, contraction, rearrangement, and fragmentation of existing ring systems, cycloadditions, transition metal-catalyzed tandem processes, and various multi-component reactions. Viable synthetic methods toward 1,5-diazocin-2-ones via direct 8-membered cyclization were also discussed along with various sources of activation by which the barrier to medium-sized ring closure to afford these compounds is surmounted.

Recently in our labs, we have become interested in employing shelf-stable 3,3-disubstituted cyclopropenes as energy-rich electrophiles to drive the cyclization of medium-sized rings and have demonstrated that such cyclizations can indeed be facilitated in the case of oxygen-based nucleophiles (Scheme 33).[58]

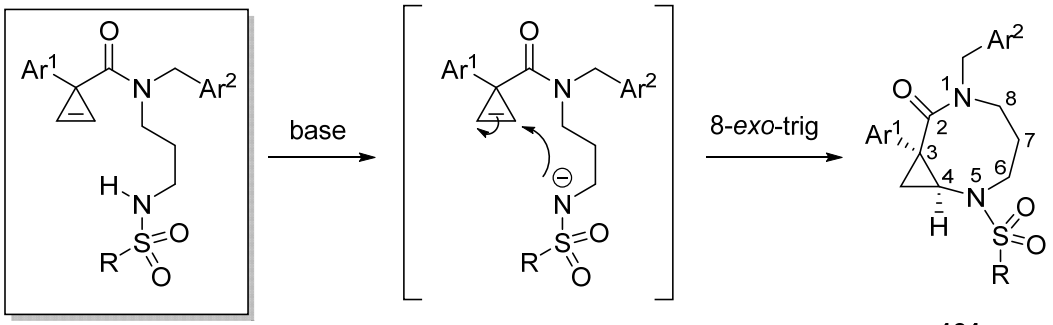
Scheme 33



126 **127** **128**

The Rubin group next became interested in synthesizing cyclopropane-fused analogs of **128** in which nitrogen nucleophiles were employed. Specifically, this thesis is concerned with the synthesis of 3,4-cyclpropane-fused 1,5-diazocin-2-ones **131** (Scheme 34). This chapter details the development of a modular synthetic route to cyclization precursors **129**.

Scheme 34



129 **130** **131**

2.2 Reactivity Trends of Cyclopropenes Toward Nucleophiles

The cyclopropene moiety is a highly-strained system due most primarily to the sp^2-hybridized carbons locked in an arrangement which constrains the carbocyclic bond angles to 60° – far from the ideal angle of 120°. This imparts an energy reserve of 53 kcal/mol.[59] This chemical potential energy can be used as a driving force for otherwise unfavorable chemical transformations.

As a very energetic class of molecules, many cyclopropenes are unstable and difficult to obtain in isolated form (Figure 5). In the presence of nucleophilic species, cyclopropenes bearing electron-withdrawing substituents on one or both olefinic carbons (Figure 5, **A**, **B**) make excellent Michael acceptors and thus are highly unstable. Most

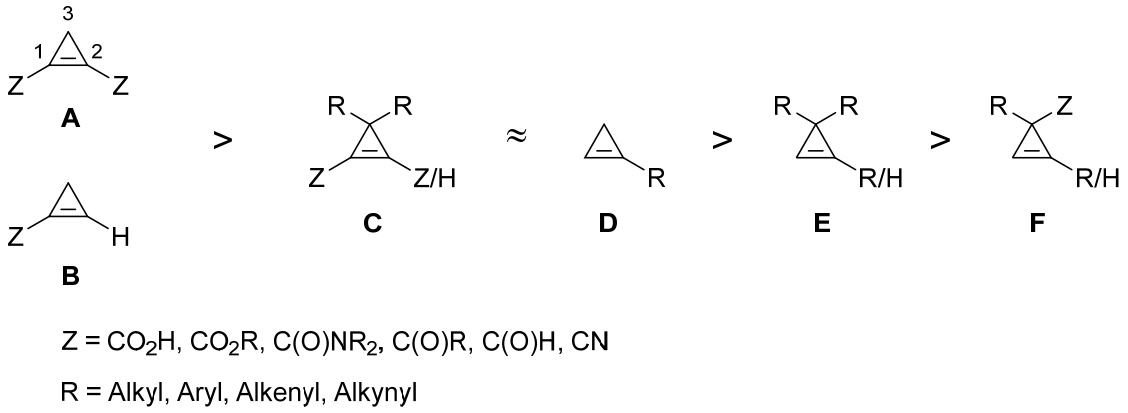


Figure 5. The reactivity of various substituted cyclopropenes toward nucleophilic attack.

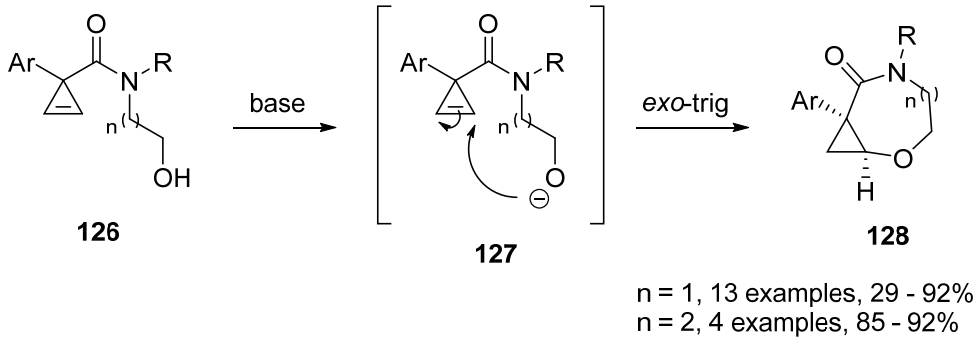
conjugated cyclopropenes of this type are not isolable and must instead be generated *in situ*. The presence of alkyl, aryl, alkenyl, or alkynyl groups at C3 mitigates this to some degree (Figure 5, **C**). This stabilization is attributed to increased steric congestion and/or electron delocalization in cases of alkenyl, alkynyl, and aryl groups. Cyclopropenes

bearing an electron donating group at C1 or C2 (Figure 5, **D**) are stabilized compared to their EWG-bearing counterparts while 3,3-disubstituted cyclopropenes (barring the copresence of a C3-EWG) are among the most stable cyclopropene species (Figure 5, **E**, **F**),[60] boasting shelf lives of several days, to months,[61] and even years if stored at low temperature under nitrogen atmosphere.[62]

2.3 Nucleophilic *exo*-trig Cyclization of 3,3-Disubstituted Cyclopropenes

Though sufficiently stable if properly handled, the double bond of pre-generated 3,3-disubstituted cyclopropenes remains highly electrophilic. Ring-retentive additions of oxygen-,[63,64] sulfur-,[65] phosphorus-,[66] as well as carbon-nucleophiles[67–70] to such substrates have all been reported. Rubin *et al*. recently disclosed a protocol for intramolecular *exo*-trig cyclization via nucleophilic attack on cyclopropenes employing alcohols as pronucleophiles to afford 1,4-oxazepan-5-ones (7-membered) and 1,4-oxazocan-5-ones (8-membered) species **128** in generally very good yields (Scheme 35).[58]

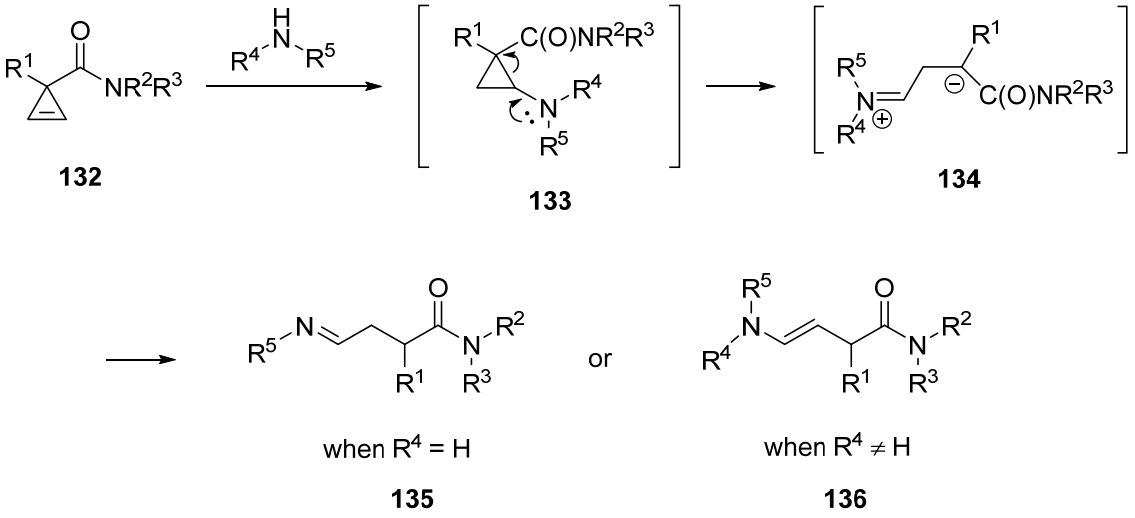
Scheme 35



2.4 Addition of Nitrogen Nucleophiles to 3,3-Disubstituted Cyclopropenes

Curious as to the reactivity of nitrogen nucleophiles toward nucleophilic cyclizations in analogous substrates, we subsequently began investigating the cyclization of nitrogen analogs of cyclopropenes **126** to form the corresponding cyclopropane-fused azalactams **131** (see Scheme 34 above). Earlier findings in the Rubin group demonstrated that 3,3-disubstituted cyclopropenes indeed undergo *inter*molecular nucleophilic addition when a simple primary or secondary amine is employed as the pronucleophile (Scheme 36).

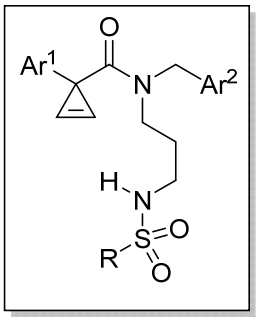
Scheme 36



However, it was observed that the amino-nitrogen of initial hydroamination product **133** was sufficiently electron-donating so as to set up a highly polarized donor-acceptor cyclopropane (DAC) system with a high propensity for ring-opening, which occurred immediately. In the presence of a proton source, the resulting zwitterionic iminium

intermediate **134** then rapidly formed imine **135** (when R^4 = H) or enamine **136** (when R ≠ H).[71]

With this in mind, it was imagined that *intra*molecular addition to such systems could be accomplished if the nucleophilic nitrogen center were sufficiently electron-deficient so as to attenuate the DAC character of the resulting cyclic products, thus mitigating the tendency for ring opening. We directed our efforts toward the synthesis of 3,3-disubstituted cyclopropene carboxamides, bearing an alkyl tether at the amide nitrogen which is terminated by an electron deficient nitrogen functionality, as precursors to 8-membered cyclopropane-fused azalactams. Given the enhanced N-H acidity of sulfonamides relative to amines, as well as their known reactivity as good nucleophiles in the case of intermolecular addition to conjugated cyclopropenes,[72] sulfonamide-terminated cyclization precursors of type **129** were targeted for synthesis (Figure 6).



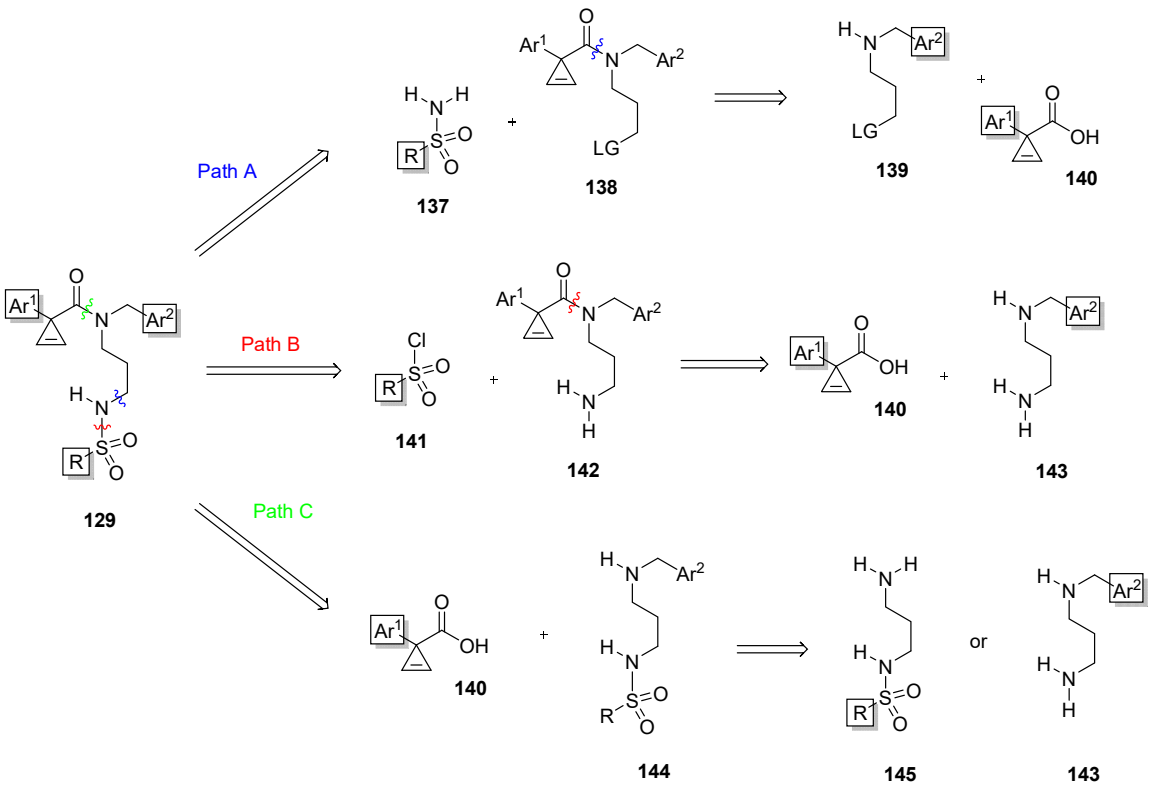
129

Figure 6: 3,3-Disubstituted cyclopropenes bearing a pro-nucleophilic sulfonamide functionality.

2.5 Synthetic Routes Toward 1,5-Diazocin-2-one Precursors

For the synthesis of cyclization precursor cyclopropenes **129**, a modular approach was desired in which various combinations of Ar^1, Ar^2, and R could be realized with relative ease by the simple variation of reagents employed in the construction of each building block. Intending to employ what has become a standard protocol[73] in the Rubin group for the conversion of cyclopropene carboxylic acids **140** to amides, several potential synthetic pathways were considered (Scheme 37).

Scheme 37



The construction of sulfonamidocyclopropene carboxamides **129** via Path A possesses the modular features desired. Secondary amine **139** would provide Ar^2 which

could be introduced easily via the reductive alkylation of inexpensive 3-halopropylamines and subsequently acylated by cyclopropene carboxylic acids **140** (providing Ar^1). The sulfonyl R-group would be born by sulfonamides **137** and incorporated via nucleophilic displacement of a leaving group (e.g. bromide) on the terminus of compound **138**. This final step would very likely be problematic as the cyclopropene double bond is highly electrophilic and would likely participate in a competing nucleophilic addition under the necessary reaction conditions.

Path B, while retaining modularity, eliminates the problem of a difficult acylation step by introducing the R-bearing sulfonyl group by way of an electrophilic species (i.e. a sulfonyl chloride **141**) so as to not to pose a threat to the fragile cyclopropene moiety. However, the acylation of cyclopropene carboxylic acid **140** is not likely to exhibit selectivity towards the secondary amino group over the primary amino group of mono-alkylated 1,3-diaminopropane **143**. Furthermore, the construction of mono-alkylated 1,3-diaminopropanes **143** themselves presents a synthetic challenge that seemed best avoided.

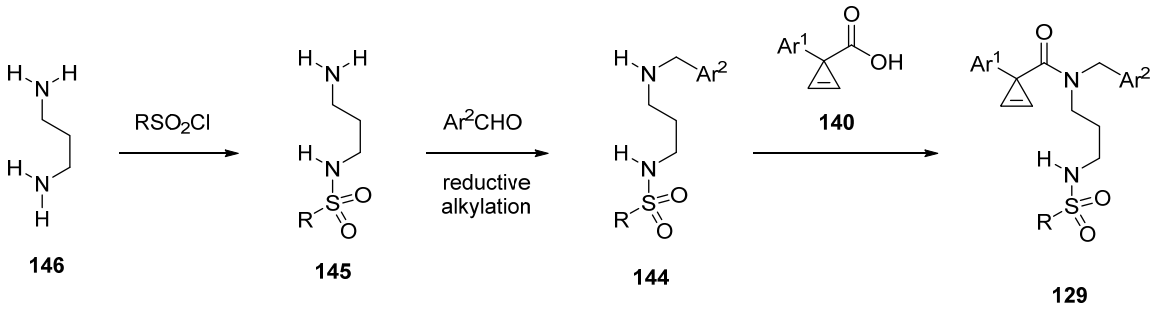
The route to cyclization precursor **129** illustrated in Path C leaves the incorporation of the cyclopropene moiety until the final step, exposing cyclopropene carboxylic acid **140** only to routinely-employed conditions which are preservative of the cyclopropene double bond. The challenge of efficient mono-functionalization of 1,3-diaminopropane – either by sulfonylation or alkylation – remains, in this case. With Path C also comes the potential of a low yielding and/or poorly chemoselective acylation of aminosulfonamide **144**. High yielding, highly chemoselective acylations of secondary alkyl amines possessing primary sulfonamido groups have been reported with common reagents such as oxalyl chloride,[74,75]

EDC,[76,77] and DCC;[78] although such reports are quite scarce. Similar reactions exhibiting modest to low yields are similarly scarce[75] and likely underreported as a result of their lack of utility. Bearing in mind the scarcity of reports and wide variation of success in the acylation of such compounds, as well as the challenges inherent to diamine mono-functionalization, efforts toward the synthesis of building blocks **129** via Path C were undertaken.

2.6 The Development of a Viable Synthetic Method Toward 8-*exo*-trig Cyclization Precursors

We embarked on the forward synthetic plan shown in Scheme 38. We first sought a simple and high-yielding method – preferably requiring little to no preparative chromatography – for obtaining differentially-functionalized 1,3-diaminopropanes **144**.

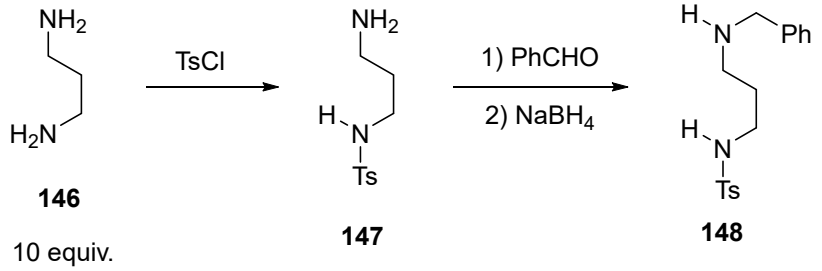
Scheme 38



The high availability of reagents capable of installing tosyl (TsCl) and benzyl (PhCHO) functional groups led us to the choice of 1,3-diaminopropane **148** as a model differentially-

functionalized diamine; to be synthesized via the mono-tosylation of 1,3-diaminopropane (**146**) in large excess followed by reductive alkylation of the extant amino functionality

Scheme 39

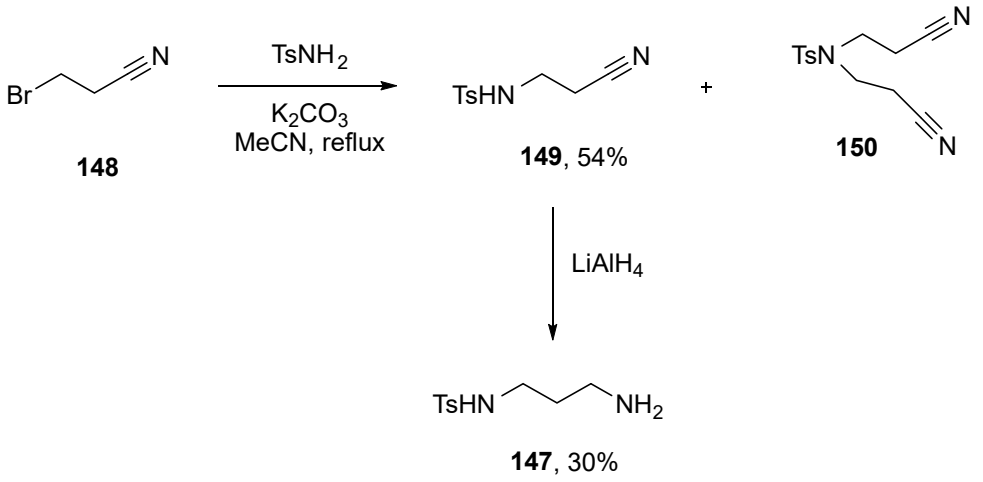


with benzaldehyde and sodium borohydride (Scheme 39). Several attempts at the mono-tosylation of 1,3-diaminopropane were all met with low isolated yield (18% maximum) – despite the adoption of reportedly successful methods[79,80] from the literature. Mono-alkylation of 1,3-diaminopropane employing a benzylhalide was not attempted as polyalkylation products would almost certainly be formed, and likely require column chromatography to obtain the desired material.[81] We then began examining alternative pathways to compound **148** which to not require the mono-sulfonylation of 1,3-diaminopropane.

Alkylation of *p*-toluenesulfonamide ($TsNH_2$) with 3-bromopropionitrile resulted in a mixture of mono- and dialkylated products which could be separated via acid-base extraction, but afforded sulfonamide **149** in only modest yield. The following lithium aluminum hydride reduction of the cyano group of nitrile **149** provided amine **147** in low (30%) yield. The overall yield for the two steps was a mere 16% – less than the yield of

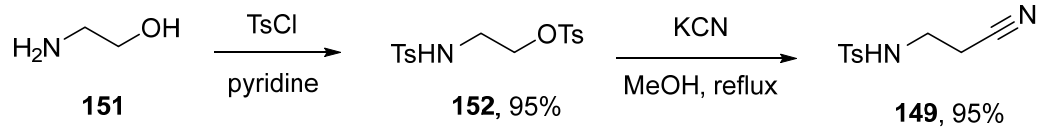
the aforementioned low yielding mono-tosylation produced in just a single step (Scheme 40).

Scheme 40



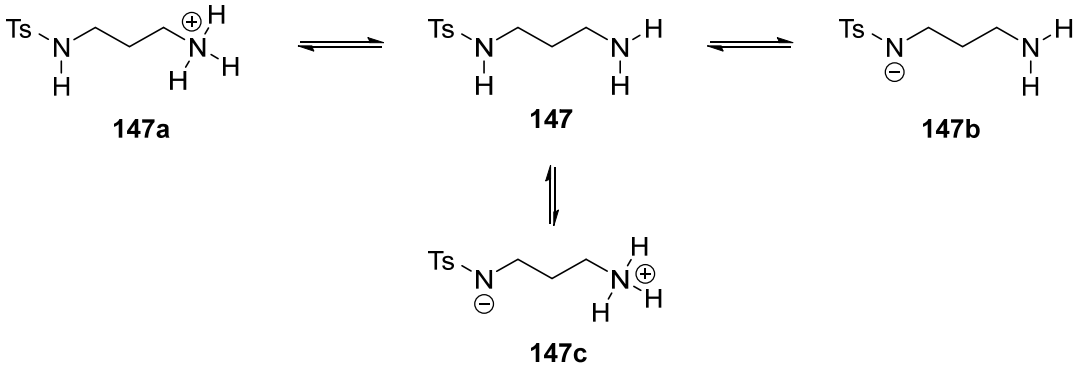
Highly efficient access to nitrile **149** was accomplished in two steps with an overall yield of 90% (Scheme 41). Bis-tosylation of 2-aminoethanol (**151**) simultaneously installed the desired terminal sulfonamide while converting the hydroxyl group into a sulfonate ester – providing an excellent leaving group for the subsequent step. Cyanide next displaced tosylate in a second high yielding step and required purification only in the form of filtration through a short plug of silica.

Scheme 41



Reduction with $LiAlH_4$ was attempted again in under various conditions on nitrile **149**. The low yields of 20-30% were puzzling and it was thought that it might be the case that material was being lost in the work-up. Given the presence of both an acidic sulfonamido group and a basic amino group, the possible forms of *N*-tosyl-1,3-diaminopropane (**147**) in aqueous media were considered (Scheme 42).

Scheme 42

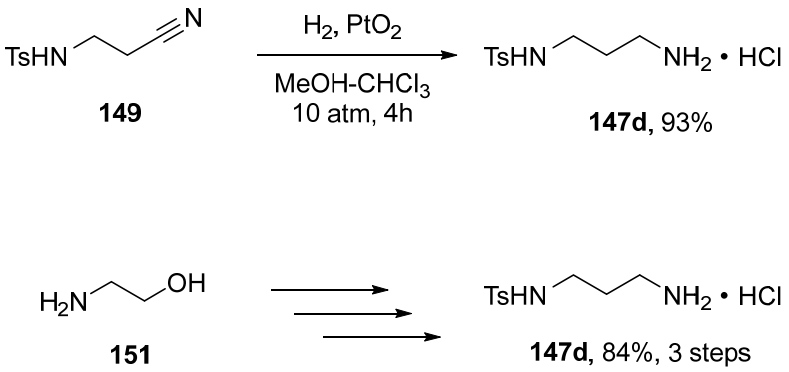


The reduction and subsequent workup was repeated multiple times employing adjustments in pH during workup, to no avail. The high solubility of **147** in water led us to attempt "water-free" quenches of the metal hydride reductions with hydrated pH-neutral salts such as sodium sulfate decahydrate so as to deprive the environment of a bulk aqueous medium for the desired compound to dissolve in. These efforts afforded no significant improvement in the yield of **147**.

In pursuit of a method for the reduction of nitrile **149** which does not involve metal hydride reducing agents nor aqueous workup, attention turned to catalytic hydrogenation as a possible means of reduction. Adapting from a known procedure[82] by Duggan *et al.*, reduction over platinum(IV) oxide in the presence of chloroform afforded the desired

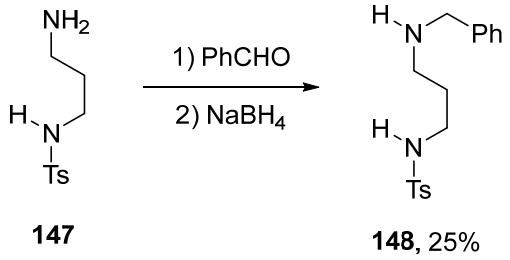
mono-tosylated amine as a hydrochloride salt in 93% yield (Scheme 43). Thus, amine hydrochloride **147d** was produced in 84% yield over three steps.

Scheme 43



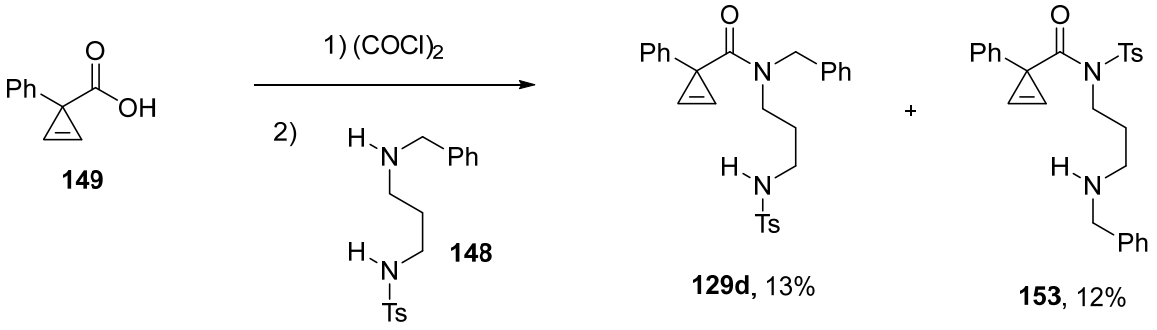
Following the synthetic logic illustrated in Scheme 40, the benzylation of **147d** was conducted via reductive alkylation with benzaldehyde followed by sodium borohydride employing triethylamine in order to allow for the formation of the free amine of **147d**. The resulting yield was lower than anticipated, affording differentially-functionalized diamine **148** with a yield of 25% (Scheme 44).

Scheme 44



Despite the unsatisfactory yield, material was now in hand for the joining of this component and a cyclopropene carboxylic acid **149**. The cyclopropene carboxylic acid bearing a phenyl group in the 3-position (i.e. Ar^1 = Ph) was chosen. The reaction proceeded with a remarkably low degree of chemoselectivity; affording the acylated amine and the acylated sulfonamides in practically equal amounts and in very low yields (Scheme 45).

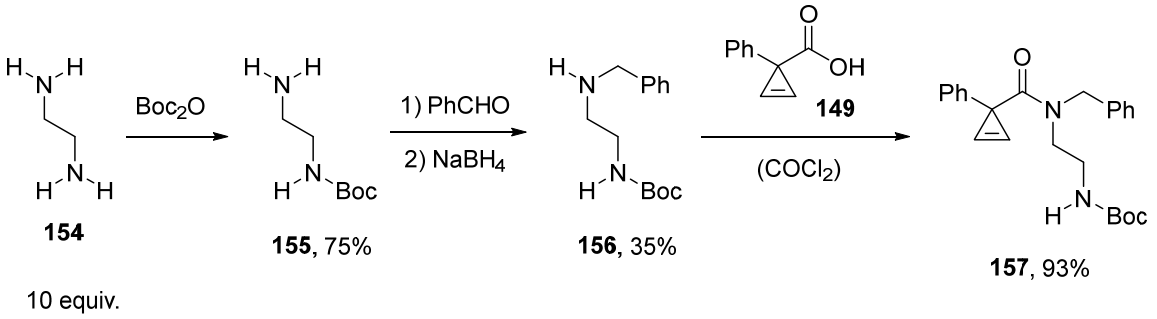
Scheme 45



Also somewhat remarkably, neither yield nor chemoselectivity changed significantly when EDC was employed as the amide coupling agent.

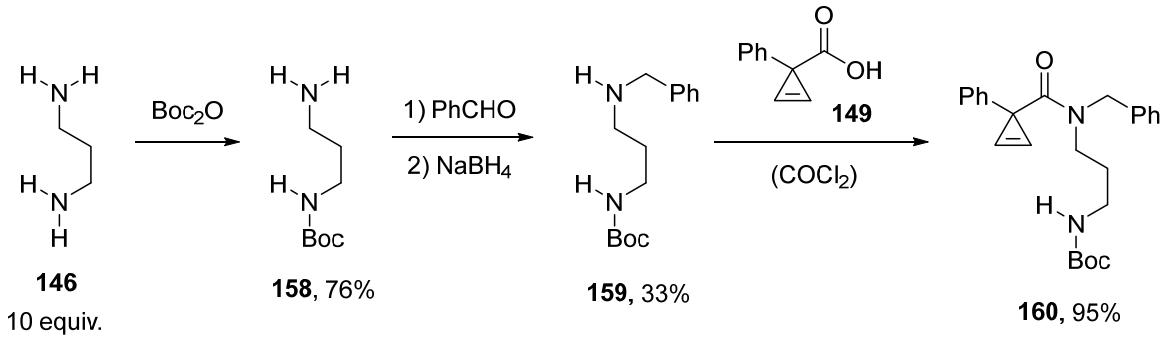
While the acylation of amine **148** was found to give poor yield and selectivity in both cases, concurrently in our lab, *tert*-butyl carbamates **157** were being prepared with relative ease via the mono-Boc protection of 1,2-diaminoethane followed by reductive alkylation, and finally acylation (Scheme 46). Though the reductive alkylation of mono-Boc-protected amine **155** exhibited low yield, the acylation of aminocarbamates **156** proceeded with exceptional yield and with no chemoselectivity issues.

Scheme 46



This lead to the consideration of accessing sulfonamide-terminated cyclopropene carboxamide **129d** via a homologous approach to that shown in Scheme 46 – using propylene diamine in place of ethylene diamine (Scheme 47). The introduction of the sulfonamido group could then be accomplished by simple deprotection-protection chemistry.

Scheme 47

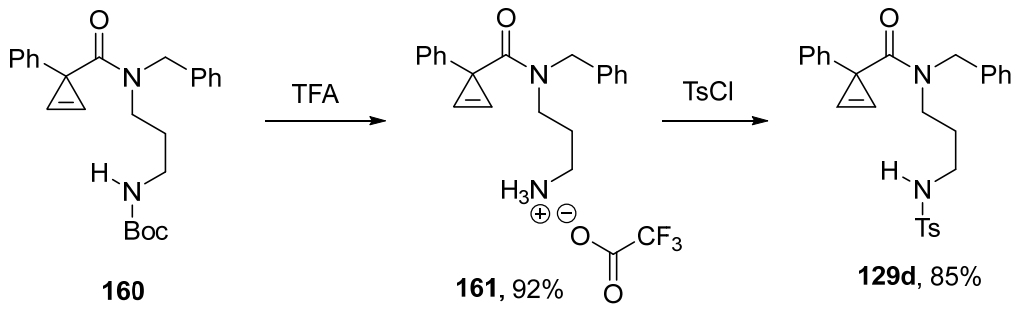


The mono-Boc-protection of 1,3-diaminopropane was much more successful than the previously discussed attempts at mono-tosylation. The borohydride reductive alkylation of mono-Boc-protected 1,3-diaminopropane **158** was as inefficient as the

homologous reductive alkylation of mono-Boc-protected 1,2-diaminoethane. Generally, the reaction sequence for synthesizing Boc-protected cyclopropene **160** (Scheme 47) afforded very similar results in each step for the synthesis of the homologous Boc-protected cyclopropene **157**.

The removal of the Boc group from cyclopropene **160** proceeded uneventfully to afford the ammonium trifluoroacetate (**161**) in high yield upon treatment with trifluoroacetic acid (Scheme 48). The subsequent tosylation of the amine nitrogen afforded the direct 8-*exo*-trig cyclization precursor in 85% yield.

Scheme 48

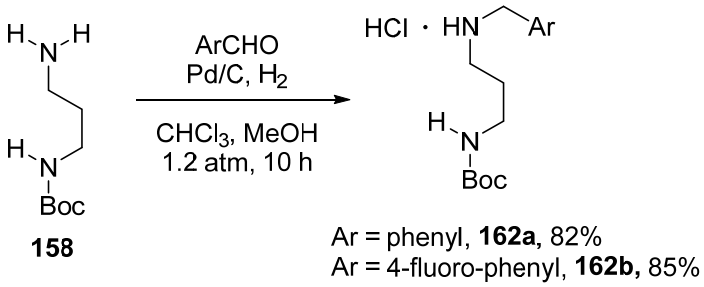


160 **161**, 92% **129d**, 85%

Though a successful synthesis of the desired cyclization precursor was achieved, the low efficiency (33% yield) of the reductive amination step still plagued the scheme. The success observed for nitrile reductions under hydrogenative conditions using a heterogeneous platinum catalyst (see Scheme 44 above) drew our attention to the possibility of performing the reductive amination entirely in a Parr type reactor using similar conditions. A search of the literature led to a 2008 report of a well-optimized, high yielding protocol of this sort. Hu *et al.* describe a "direct reductive amination" (DRA) of benzaldehydes.[83] DRA is conducted under 1-2 atm hydrogen over palladium on carbon

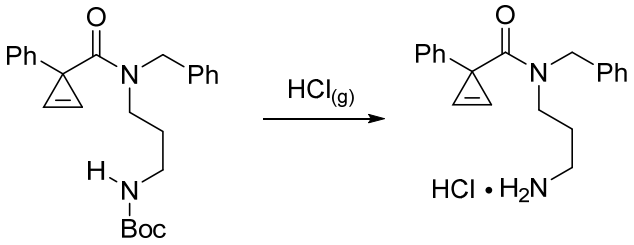
using chloroform as an additive. The authors propose that chloroform undergoes a hydrodechlorination to afford hydrogen chloride which immediately poisons the 'active palladium catalyst', converting it into a species that is highly selective toward the reduction of imines in the presence of aldehydes. In addition, the generated HCl protonates the amine product allowing for easy isolation via filtration. Subjecting amine **158** to similar conditions afforded the corresponding amine hydrochloride in good yield – 82% compared to 33% with conventional borohydride reductive amination (Scheme 49). The reaction was shown to provide similar yield when 4-fluorobenzaldehyde was used in place of benzaldehyde.

Scheme 49



It was also found that ammonium trifluoroacetate salt **161**, although produced in high yield, started to exhibit signs of decomposition, in the form of a color change, within just a few hours after synthesis. Within 3-4 days, known reactions employing this material began to exhibit significant decreases in yield.

Scheme 50

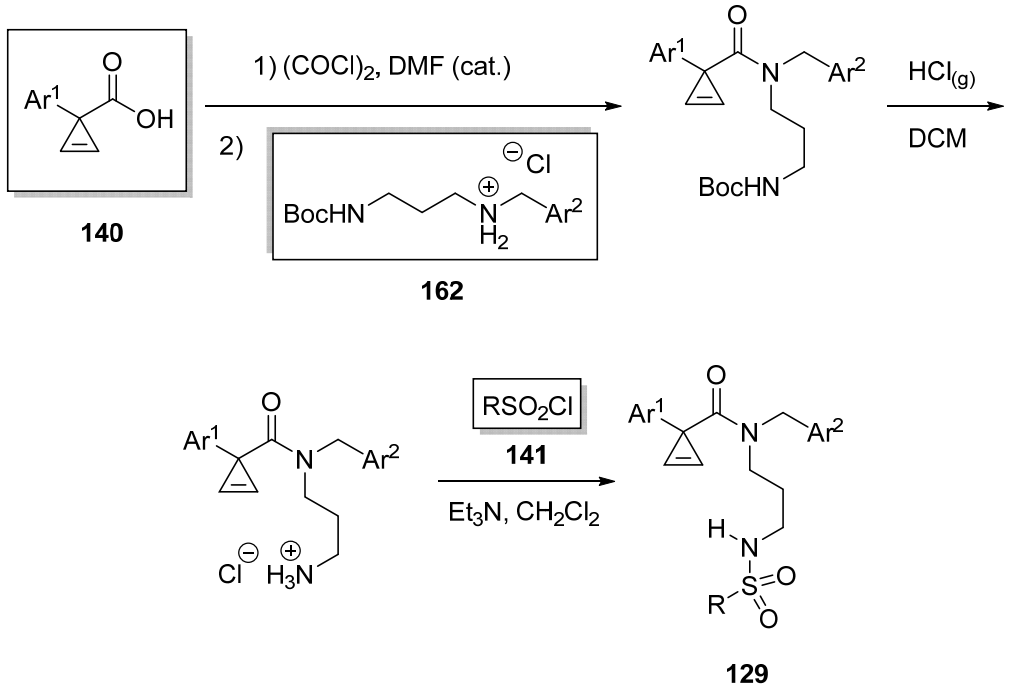


160

163, 79%

For best results, the material was used immediately after its synthesis and concentration. In an effort to eliminate this problem, another avenue was explored for the Boc-deprotection of cyclopropene **160**. Known to be a suitable agent for removing Boc from nitrogen atoms, hydrogen chloride was considered. The bubbling of HCl gas through a solution of **160** in dichloromethane afforded, after a simple work-up, amine hydrochloride **163** (Scheme 50). The salt was produced with a lower – although still satisfactory – yield and proved to be much more stable and also easier to work with. Compound **163** can be stored under no special conditions for many months without any noticeable degradation. Scheme 51 illustrates an effective synthetic pathway to cyclization precursors **129**.

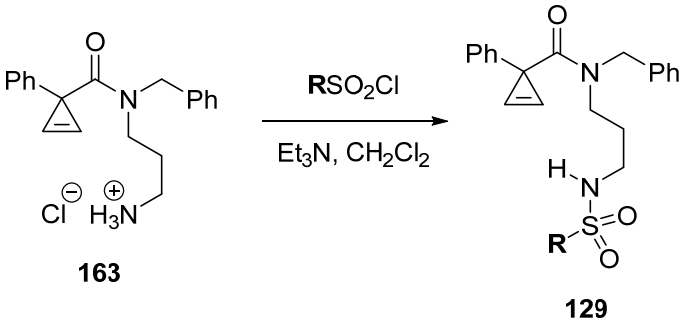
Scheme 51



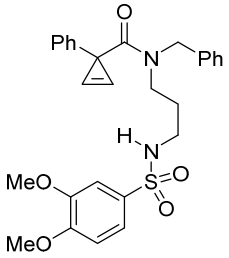
2.7 Examples of Pronucleophilic 8-*exo*-trig Cyclization Precursors

With a working method in hand for the synthesis of sulfonamide-terminated cyclization precursors of type **129**, variation of the group R (i.e. sulfonyl group) was explored (Figure 7). Yields ranged from 55-88%, exhibiting no noticeable trend with respect to the electronic nature of the sulfonamides employed. Further, no trend with respect the steric nature of the sulfonamides was observed.

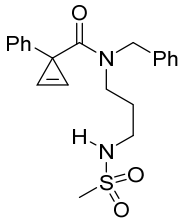
Figure 7: Synthesized examples of sulfonamide precursors to 8-*exo*-trig cylization.



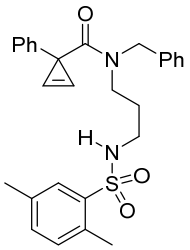
163 **129**



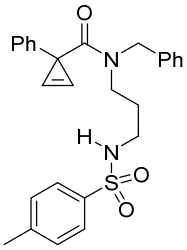
129a, 60%



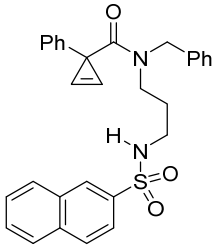
129b, 59%



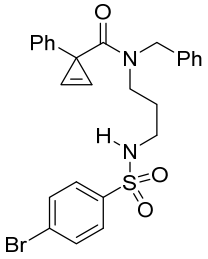
129c, 57%



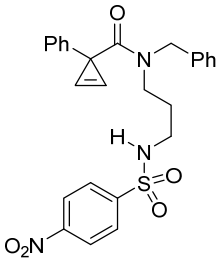
129d, 88%



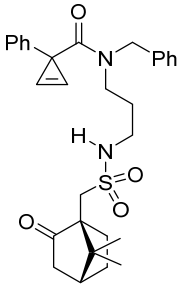
129e, 67%



129f, 55%



129g, 83%



129h, 57%

2.8 Conclusion

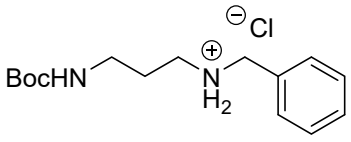
A protocol for the synthesis of pronucleophilic 8-*exo*-trig cyclization precursors **129** has been reported. Utilizing this approach, it is possible to synthesize a diverse range of cyclopropenes **129** featuring varying Ar^1, Ar^2, and R groups in many combinations by the use of 3,3-disubstituted cyclopropenes **140**, 2° amine hydrochlorides **162**, and sulfonyl chlorides **141** as building blocks. Several examples of compounds, in which the R group is varied, have been successfully synthesized and reported. The tolerance of this synthetic pathway to differentiation of building blocks **140** and **162** remains to be explored.

2.9 Experimental

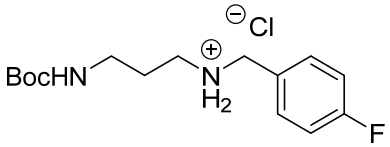
2.9.1 General Information

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (–) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR Spectrometer. HRMS was carried out on an LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried under vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 μm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 μm) were used for TLC analysis. Anhydrous DCM, THF, 1,4-dioxane, DME, MTBE, acetonitrile, and toluene were each prepared by refluxing commercially-available solvent over CaH_2 followed by distillation under a stream of dry nitrogen at ambient pressure and stored over 4Å molecular sieves under dry nitrogen. Anhydrous DMSO and DMF were prepared by stirring at 100 °C and 80 °C, respectively, over CaH_2 followed by distillation under reduced pressure stored over 4Å molecular sieves under dry nitrogen. All reagents, unless otherwise specified were used in their commercially-available forms and purities. All manipulations of KOH and/or 18-crown-6 were conducted under inert atmosphere (<8 ppm residual oxygen and moisture) using a combination of glovebox and standard Schlenk techniques.

2.9.2 Synthesis of Diamines



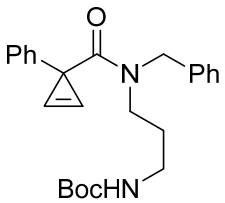
***N*-Benzyl-3-((*tert*-butoxycarbonyl)amino)propan-1-aminium chloride** (**162a**): A 15 mL autoclave vessel was charged with *tert*-butyl (3-(benzylamino)propyl)carbamate (400 mg, 2.30 mmol, 1 equiv.), benzaldehyde (279 μL, 2.75 mmol, 1.2 equiv.), 10 wt% palladium on carbon (29.3 mg, 7.3 wt%), methanol (3.5 mL), and chloroform (230 μL, 2.85 mmol, 1.24 equiv.). The mixture was stirred at 750 RPM under hydrogen gas (1.4 atm) for 10 hours. The catalyst was removed by vacuum filtration through Celite® 545 non-acid-washed filter aid washing with methanol. Volatiles were removed under reduced pressure. The resultant solid was triturated with diethyl ether and collected via vacuum filtration to afford the title compound as a white powder (565 mg, 1.88 mmol, 82%); mp 148.2 – 150.1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 2H), 7.57 – 7.51 (m, 2H), 7.46 – 7.38 (m, 3H), 6.95 (t, J = 6.0 Hz, 1H), 4.12 (s, 2H), 2.98 (q, J = 6.5 Hz, 2H), 2.86 (t, J = 7.9 Hz, 2H), 1.76 (p, J = 6.9 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.7, 132.0, 130.0 (+), 128.9 (+), 128.6 (+), 77.8, 49.9 (–), 44.4 (–), 37.0 (–), 28.2 (–), 26.2 (–); FT IR (KBr, cm^{-1}): 3368, 3338, 2977, 2941, 2766, 1687, 1531, 1457, 1368, 1289, 1175, 753, 698; HRMS (TOF ES): found 265.1910, calculated for $C_{15}H_{25}N_2O_2$ (M+) 265.1916 (2.3 ppm).



3-((*tert*-Butoxycarbonyl)amino)-*N*-(4-fluorobenzyl)propan-1-aminium chloride (**162b**): A 15 mL autoclave vessel was charged with *tert*-butyl (3-(benzylamino)propyl)carbamate (200 mg, 1.15 mmol, 1 equiv.), 4-fluorobenzaldehyde

(148 μL, 1.38 mmol, 1.2 equiv.), 10 wt% palladium on carbon (14.7 mg, 7.3 wt%), methanol (1.5 mL), and chloroform (114 μL, 1.42 mmol, 1.24 equiv.). The mixture was stirred at 750 RPM under hydrogen gas (1.4 atm) for 10 hours. The catalyst was removed by vacuum filtration through Celite® 545 non-acid-washed filter aid washing with methanol. Volatiles were removed under reduced pressure. The resultant solid was triturated with hot ethyl acetate and collected via vacuum filtration. Diamine dihydrochloride side product was selectively crystallized out in ethanol. The mother liquor was concentrated to afford the title compound as a pale yellow powder (311 mg, 0.98 mmol, 85%); mp 187.4 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.02 (br s, 2H), 7.58 (dd, J = 8.2, 5.5 Hz, 2H), 7.28 (t, J = 8.9 Hz, 2H), 6.96 (t, J = 5.9 Hz, 1H), 4.12 (s, 2H), 2.98 (q, J = 6.4 Hz, 2H), 2.85 (s, 2H), 1.74 (p, J = 7.8 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 162.37 (d, J_{CF} = 245.6 Hz, 1C), 155.71, 132.45 (d, J_{CF} J = 8.4 Hz, 2C, (+)), 128.30 (d, J_{CF} = 2.6 Hz, 1C), 115.48 (d, J_{CF} = 21.4 Hz, 2C, (+)), 77.74, 49.08 (–), 44.27 (–), 36.99 (–), 28.20 (+), 26.26 (–); ^{19}F NMR (471 MHz, DMSO-d_6) δ ppm -112.83 – -112.91 (m); FT IR (KBr, cm^{-1}): 3362, 2980, 2945, 2777, 2699, 2567, 2412, 1680, 1516, 1443, 1368, 1287, 1225, 1170, 990, 833; HRMS (TOF ES): found 283.1831, calculated for $C_{15}H_{24}FN_2O_2$ (M+) 283.1822 (3.2 ppm).

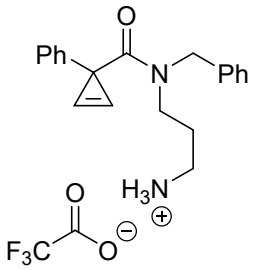
2.9.3 Synthesis of Cyclopropene Carboxamides



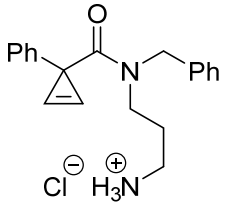
***tert*-Butyl (3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (160)**: A flame-dried round bottom flask was charged with 1-phenylcycloprop-2-ene-1-carboxylic acid (760 mg, 4.74 mmol, 1.00 equiv.), anhydrous dichloromethane (21.3 mL), and DMF (5

drops) under nitrogen atmosphere. Oxalyl chloride (623 μL, 903 mg, 7.12 mmol, 1.5 equiv.) was then added dropwise and the mixture was stirred at room temperature for 2h. Volatiles were removed under reduced pressure to provide the crude acyl chloride. To a flame-dried flask containing *tert*-butyl (3-(benzylamino)propyl)carbamate hydrochloride (**162a**) (1.65 g, 5.48 mmol, 1.16 equiv.), triethylamine (1.984 mL, 1.44 g, 14.23 mmol, 3 equiv.), and anhydrous dichloromethane (9.2 mL) was added dropwise a solution of the crude acyl chloride in anhydrous dichloromethane (6.1 mL). The reaction mixture was stirred for 16 hours at RT. The mixture was diluted with dichloromethane (40 mL) and washed with 1N HCl (3 x 30 mL). The combined aqueous washes were back-extracted with dichloromethane (1 x 30 mL). The combined organic layers were then washed with brine (1 x 20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel eluting with DCM:EtOAc (7:1) to afford the title compound as a pale yellow oil (1.83 g, 4.50 mmol, 95%); R_f 0.36 (DCM:EtOAc, 7:1); NMR spectra indicate the presence of two rotamers (ratio of 2.6:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm [7.35 (s) & 7.33-7.12 (m) & 7.13 (d, J = 7.1 Hz) & 7.09 (s) & 6.94 (d, J = 6.9 Hz) , Σ12H], [5.45 (t, J = 6.3 Hz) & 4.61 (s) & 4.49 (s) & 4.27 (m), Σ3H], [3.37 (t, J = 6.7 Hz) & 3.23 (m), Σ2H], [3.13 (q, J = 6.3 Hz) & 2.79 (q, J = 6.5 Hz), Σ2H], [1.66 (p, J = 6.5 Hz) & 1.41 (m), Σ11H]; ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 175.1, 174.4, 156.2, 155.9, 143.3, 143.0, 137.6, 137.0, 128.9 (+), 128.8 (+), 128.7 (+), 128.6 (+), 128.3 (+), 127.7 (+), 127.5 (+), 126.9 (+), 126.8 (+), 126.7 (+), 126.4 (+), 126.0 (+), 110.4 (+), 109.9 (+), 79.4, 79.1, 51.3 (–), 47.6 (–), 44.6 (–), 42.1 (–), 38.0 (–), 37.7 (–), 32.3, 32.1, 28.6 (+), 28.5 (+), 28.5 (–), 27.6 (–); FT IR (NaCl, cm^{-1}): 3334, 3085, 3061, 3028, 2976, 2931, 1708, 1623, 1514, 1495, 1452, 1425, 1365, 1273, 1250, 1171,

997, 737, 700, 654, 605; HRMS (TOF ES): found 429.2149, calculated for $C_{25}H_{30}N_2O_3$ (M+Na) 429.2154 (1.2 ppm).

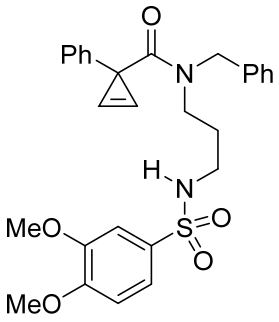


3-(*N*-Benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium trifluoroacetate (**161**): *tert*-Butyl (3-(N-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (**156**) (1.80 g, 4.43 mmol, 1 equiv.) was dissolved in dichloromethane (9.7 mL). The solution was cooled to 0 °C and trifluoroacetic acid (9.7 mL) was added. The reaction mixture was then stirred at RT for 4 hours. Volatiles were removed under reduced pressure to afford the crude trifluoroacetate salt as a light brown oil (1.71 g, 4.08 mmol, 92%). The material was used without further purification.



3-(*N*-Benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (163): Gaseous hydrogen chloride was bubbled through a solution of (3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (**156**) (589 mg, 1.45 mmol) in dichloromethane (25 mL) while stirring at rt. The reaction was allowed to proceed until TLC analysis indicated consumption of the protected amine (45 min). Volatiles were removed under reduced pressure. The resultant solid was triturated with diethyl ether and collected via vacuum filtration to afford the title compound as a white crystalline solid (390 mg, 1.14 mmol, 79%); mp 89.1 °C (decomposed); NMR spectra indicate the presence of two rotamers (ratio of 1.4:1): ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ [7.93 (s) & 7.89 (s) & 7.62 (s), Σ5H], [7.38 –

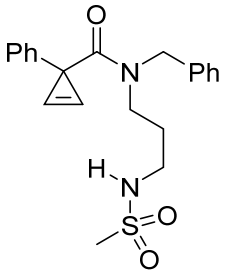
7.17 (m) & 7.12 – 7.05 (m) & 7.01 – 6.98 (m), Σ10H], [4.54 (s) & 4.52 (s), Σ2H], [3.26 (t, J = 7.9 Hz) & 3.21 (t, J = 7.2 Hz), Σ2H], [2.71 (q, J = 6.6 Hz) & 2.54 (q, J = 6.4 Hz), Σ2H], [1.78 (p, J = 7.4 Hz) & 1.72 – 1.64 (m), Σ2H]; FT IR (NaCl, cm^{-1}): 3122, 3084, 2817, 2788, 2712, 1590, 1531, 1441, 1430, 1367, 1242, 738, 709, 696, 662, 537; HRMS (TOF ES): found 307.1827, calculated for $C_{20}H_{23}N_2O$ (M+) 307.1810 (5.5 ppm).



_N_-Benzyl-_N_-(3-((3,4-dimethoxyphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129a**):

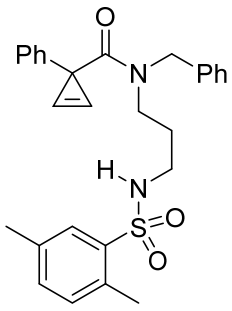
Typical Procedure: An oven-dried 5 mL V-vial equipped with a magnetic spin vane was charged with 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (94 mg, 0.274 mmol, 1 equiv.), dichloromethane (1.5 mL), and triethylamine (115 µL, 83 mg, 0.822 mmol, 3 equiv.). The solution was cooled to 0 °C and 3,4-dimethoxybenzenesulfonyl chloride (68.0 mg, 0.287 mmol, 1.05 equiv.) was added in a single portion. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was then stirred for an additional 16 hours at RT. The reaction mixture was diluted with dichloromethane (20 mL) and washed successively with 1M HCl (2 x 6 mL), 5% $NaHCO_3$ (2 x 6 mL), water (2 x 6 mL), and brine (1 x 8 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel eluting with DCM:EtOAc (3:1) to afford the title compound as a thick, colorless oil (83 mg, 0.164 mmol, 60%); R_f = 0.26 (DCM:EtOAc, 3:1) NMR spectra indicate the presence of two rotamers (ratio of 8:1): ^{1}H NMR (500 MHz,

$CDCl_3$) δ ppm [7.52 (dd, *J* = 8.4, 2.1 Hz) & 7.39 (d, *J* = 2.1 Hz) & 7.38 – 7.17 (m) & 7.09 (s) & 6.97 (dd, *J* = 6.9, 2.8 Hz) & 6.93 – 6.88 (m), Σ15H], [6.08 (t, *J* = 5.5 Hz) & 4.59 (s) & 4.44 (s), 3.94 (s) & 3.93 (s) & 3.90 (s) & 3.60 (t, *J* = 5.9 Hz), Σ9H], [3.37 (t, *J* = 6.2 Hz) & 3.33 – 3.23 (m), Σ2H], [2.92 (q, *J* = 5.8 Hz) & 2.55 (q, *J* = 6.3 Hz), Σ2H], [1.62 (p, *J* = 6.2 Hz) & 1.37 – 1.32 (m), Σ2H]; ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 175.6, 152.4, 149.2, 142.7, 136.4, 132.3, 129.0 (+), 128.8 (+), 128.7 (+), 128.2 (+), 127.9 (+), 126.9 (+), 126.9 (+), 126.7 (+), 126.0 (+), 121.1 (+), 110.6 (+), 110.1 (+), 109.9 (+), 100.1, 56.4 (+), 56.3 (+), 51.2 (–), 47.7 (–), 44.4 (–), 41.4 (–), 40.1 (–), 32.0, 29.9 (+), 27.3 (+). FT IR (NaCl, cm^{-1}): 3269, 3148, 3103, 3061, 2934, 2856, 1613, 1509, 1443, 1325, 1262, 1237, 1182, 1153, 1095, 1021, 765, 701, 578; HRMS (TOF ES): found 529.1759, calculated for $C_{28}H_{30}N_2O_5S$ (M+Na) 529.1773 (2.6 ppm).



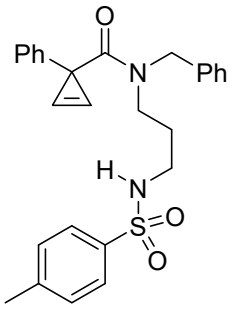
***N*-Benzyl-*N*-(3-(methylsulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129b**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (167 mg, 0.487 mmol, 1 equiv.), triethylamine (204 μL, 148 mg, 1.46 mmol, 3 equiv.), and methanesulfonyl chloride (40 μL, 57 mg, 0.511 mmol, 1.05 equiv.) to yield the title compound as a thick, colorless oil (110 mg, 0.286 mmol, 59%); R_f = 0.29 (DCM:EtOAc, 2:3); NMR spectra indicate the presence of two rotamers (ratio of 6.9:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.42 (s) & 7.39 – 7.22 (m), Σ8H], [7.17 – 7.12 (m) & 6.99 – 6.94 (m), Σ3H], [5.85 (s) & 4.65 (s) & 4.55 (s), Σ3H], [3.54 (t, *J* = 6.1 Hz) & 3.47 (t, *J* = 6.2 Hz) &

3.38 – 3.32 (m) & 3.15 (t, J = 6.1 Hz), Σ4H], [3.07 – 3.01 (m) & 2.97 (s) & 2.80 (s) & 2.77 – 2.71 (m), Σ3H], [1.73 (p, J = 6.1 Hz) & 1.46 (p, J = 6.8 Hz), Σ2H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 174.4, 143.2, 142.7, 137.4, 136.3, 129.2 (+), 128.9 (+), 128.8 (+), 128.7 (+), 128.6 (+), 128.1 (+), 127.8 (+), 126.9 (+), 126.8 (+), 126.6 (+), 126.3 (+), 125.9 (+), 110.3 (+), 110.0 (+), 51.4 (–), 47.6 (–), 44.3 (–), 41.6 (–), 40.5 (–), 40.4 (+), 40.2 (–), 40.0 (+), 32.2, 31.9, 28.4 (–), 28.0 (–); FT IR (NaCl, cm^{-1}): 3259, 3062, 3030, 2932, 1721, 1623, 1453, 1319, 1150, 1079, 975, 735, 702, 521; HRMS (TOF ES): found 407.1414, calculated for $C_{21}H_{24}N_2O_3S$ (M+Na) 407.1405 (2.2 ppm).



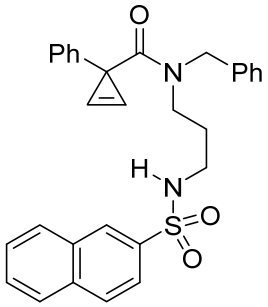
***N*-benzyl-*N*-(3-((2,5-dimethylphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (129c)**: The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (115 mg, 0.274 mmol, 1 equiv.), triethylamine (114 μL, 83 mg, 0.821 mmol, 3 equiv.), and 2,5-dimethylbenzenesulfonyl chloride (59 mg, 0.287 mmol, 1.05 equiv.) to yield the title compound as a thick, colorless oil (73.9 mg, 0.156 mmol, 57%); R_f = 0.35 (6:1, DCM:EtOAc); NMR spectra indicate the presence of two rotamers (ratio of 5.9:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.79 (d, J = 1.9 Hz) & 7.67 (s), Σ1H], [7.36 (s) & 7.32 – 7.15 (m) & 7.13 (s) & 7.07 – 7.03 (m) & 6.93 – 6.89 (m), Σ14H], [6.09 (t, J = 6.8 Hz) & 4.58 (s) & 4.44 (s) & 3.77 (t, J = 6.3 Hz), Σ3H], [3.38 (t, J = 6.2 Hz) & 3.30 – 3.23 (m), Σ2H], [2.94 (q, J = 6.3 Hz) & 2.67 (s) & 2.51 (q, J = 6.5 Hz) & 2.47 (s) & 2.36 (s), Σ8H], [1.57 (p, J = 6.1 Hz) & 1.33 (p, J = 6.7 Hz), Σ2H]; ^{13}C NMR (126 MHz, $CDCl_3$)

δ 175.6, 174.5, 142.8, 138.4, 136.5, 136.3, 136.0, 135.5, 134.2, 133.7 (+), 133.2 (+), 132.6 (2C, (+)), 130.1 (+), 129.8 (+), 129.6, 129.0 (+), 128.8 (2C, (+)), 128.7 (+), 128.2 (+), 127.9 (+), 127.5 (+), 127.0 (+), 126.9 (+), 126.8 (+), 126.7 (+), 126.1 (+), 110.4 (+), 110.2 (+), 51.2 (–), 47.6 (–), 44.4 (–), 41.4 (–), 40.3 (–), 39.9 (–), 32.4, 32.1, 28.0 (–), 27.6 (–), 21.0 (+), 20.0 (+), 19.9 (+); FT IR (NaCl, cm^{-1}): 3142, 3100, 3053, 3028, 2927, 2869, 1614, 1451, 1427, 1207, 1151, 1095, 816, 738, 701, 682, 655, 594; HRMS (TOF ES): found 497.1872, calculated for $C_{28}H_{30}N_2O_3S$ (M+Na) 497.1875 (0.6 ppm).



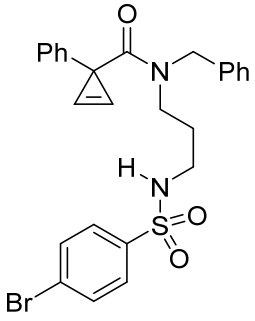
***N*-benzyl-N-(3-((4-methylphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129d**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (163 mg, 0.475 mmol, 1 equiv.), triethylamine (199 µL, 144 mg, 1.43 mmol, 3 equiv.), and 4-methylbenzenesulfonyl chloride (95 mg, 0.499 mmol, 1.05 equiv.) to yield the title compound as a thick, colorless oil (193 mg, 0.419 mmol, 88%). R_f = 0.32 (DCM:EtOAc, 6:1); NMR spectra indicate the presence of two rotamers (ratio of 5.6:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm [7.79 (d, *J* = 8.2 Hz) & 7.61 (d, *J* = 8.0 Hz), Σ2H], [4.78 (s) & 7.32–7.16 (m) & 7.11 (s) & 7.01-6.95 (m) & 6.90 (d, *J* = 6.9 Hz) & 6.06 (t, *J* = 6.6 Hz), Σ14H], [6.06 (t, *J* = 6.6 Hz) & 4.57 (s) & 4.43 (s) & 3.74 (t, *J* = 6.2 Hz), Σ3H], [3.36 (t, *J* = 6.2 Hz) & 3.26 (m), Σ2H], [2.91 (q, *J* = 6.3 Hz) & 2.54 (q, *J* = 6.2 Hz), Σ2H], [2.42 (s), 2.40 (s), [1.60 (p, *J* = 6.1 Hz) & 1.34 (p, *J* = 6.7 Hz), Σ2H]; ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 175.6, 143.1, 142.8, 129.9 (+), 129.8 (+), 129.0 (+), 128.8 (+), 128.7

(+), 128.7 (+), 128.2 (+), 127.9 (+), 127.5 (+), 127.3 (+), 127.1 (+), 127.0 (+), 126.8 (+), 126.7 (+), 126.6 (+), 126.0 (+), 110.4 (+), 110.2 (+), 51.2 (–), 47.6 (–), 44.4 (–), 41.4 (–), 40.5 (–), 40.1 (–), 32.0 (–), 28.0 (–), 27.3 (–), 21.6 (+); FT IR (KBr, cm^{-1}): 3147, 3103, 3061, 3028, 2925, 2869, 1612, 1445, 1426, 1207, 1152, 1093, 815, 738, 700, 658, 551; HRMS (TOF ES): found 483.1736, calculated for $C_{27}H_{28}N_2O_3S$ (M+Na) 483.1718 (3.7 ppm).



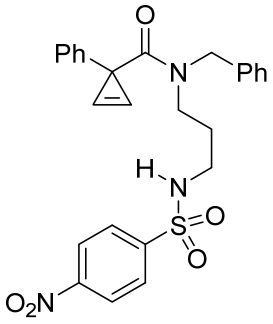
***N*-benzyl-*N*-(3-(naphthalene-2-sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129e**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (115 mg, 0.335 mmol, 1 equiv.), triethylamine (140 µL, 102 mg, 1.00 mmol, 3 equiv.), and naphthalene-2-sulfonyl chloride (84 mg, 0.369 mmol, 1.05 equiv.) to yield the title compound as a thick, colorless oil (112 mg, 226 mmol, 67%). R_f = 0.33 (DCM:EtOAc, 6:1); NMR spectra indicate the presence of two rotamers (ratio of 5.6:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ [8.46 (s) & 8.32 (s), Σ2H], [7.97 – 7.86 (m) & 7.71 – 7.54 (m), Σ6H], [7.34 – 7.21 (m) & 7.19 – 6.99 (m) & 6.95 – 6.92 (m) & 6.87 (dd, *J* = 7.4, 2.1 Hz), Σ12H], [6.30 (t, *J* = 6.7 Hz) 4.56 (s) & 4.40 (s) & 3.83 (t, *J* = 6.5 Hz), Σ3H], [3.37 (t, *J* = 6.2 Hz) & 3.28 – 3.22 (m), Σ2H], [2.95 (q, *J* = 6.0 Hz) & 2.57 (q, *J* = 6.4 Hz), Σ2H], [1.59 (p, *J* = 6.1 Hz) & 1.34 (p, *J* = 6.7 Hz), Σ2H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 142.6, 137.5, 136.4, 134.9, 132.4, 129.7 (+), 129.5 (+), 129.4 (+), 129.3 (+), 129.2 (+), 129.1 (+), 129.0 (+), 128.9 (+), 128.7 (2C, (+)) 128.6 (+),

128.5 (+), 128.3 (+), 128.3 (+), 128.2 (+), 128.0 (+), 127.9 (+), 127.5 (+), 127.1 (+), 127.0 (+), 126.8 (+), 126.7 (+), 126.4 (+), 126.0 (+), 122.8 (+), 122.3 (+), 110.4 (+), 110.2 (+), 51.2 (–), 47.6 (–), 44.4 (–), 41.4 (–), 40.6 (–), 40.1 (–), 32.4, 32.0, 28.0 (–), 27.3 (–); FT IR (NaCl, cm^{-1}): 3276, 3149, 3105, 3058, 3029, 2935, 2872, 1611, 1494, 1425, 1328, 1267, 1157, 1131, 1076, 818, 735, 700, 616, 550, 478; HRMS (TOF ES): found 519.1734, calculated for $C_{30}H_{28}N_2O_3S$ (M+Na) 519.1718 (3.1 ppm).



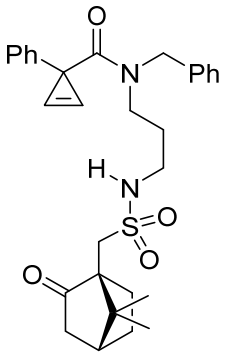
***N*-benzyl-N-(3-((4-bromophenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129f**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (122 mg, 0.356 mmol, 1 equiv.), triethylamine (149 μL, 108 mg, 1.07 mmol, 3 equiv.), and 4-bromobenzenesulfonyl chloride (**163**) (95 mg, 0.374 mmol, 1.05 equiv.) to yield the title compound as a colorless oil (102 mg, 0.194 mmol, 55%); R_f = 0.28 (hexanes:EtOAc:MeOH, 7:2:1); NMR spectra indicate the presence of two rotamers (ratio of 7.9:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm [7.77 – 7.73 (m) & 7.63 – 7.55 (m), Σ4H], [7.36 (s) & 7.32 – 7.14 (m) & 7.11 (s) & 7.01 – 6.96 (m) & 6.91 – 6.87 (m), Σ12H], [6.37 (t, *J* = 6.6 Hz) & 4.57 (s) & 4.45 (s) & 4.19 (t, *J* = 6.4 Hz), Σ3H], [3.36 (t, *J* = 6.2 Hz) & 3.30 – 3.23 (m), Σ2H], [2.90 (q, *J* = 6.1 Hz) & 2.53 (q, *J* = 6.3 Hz), Σ2H], [1.60 (p, *J* = 6.1 Hz & 1.37 (p, *J* = 6.6 Hz), Σ2H]; ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 175.9, 174.9, 143.1, 142.5, 139.6, 138.8, 137.2, 136.1, 132.5 (+), 132.4 (+), 129.0 (+),

128.9 (+), 128.8 (+), 128.8 (+), 128.7 (+), 128.6 (+), 128.2 (+), 128.0 (+), 127.6 (+), 127.0 (+), 126.8 (+), 126.6 (+), 125.9 (+), 110.3 (+), 110.1 (+), 51.4 (–), 47.7 (–), 44.4 (–), 41.6 (–), 40.5 (–), 40.1 (–), 32.2, 31.9, 27.9 (–), 27.3 (–); FT IR (NaCl, cm^{-1}): 3262, 3149, 3105, 3062, 3029, 2933, 2872, 1612, 1576, 1494, 1426, 1357, 1163, 1010, 823, 736, 700, 654, 605, 562; HRMS (TOF ES): found 547.0645, calculated for $C_{26}H_{25}BrN_2O_3S$ (M+Na) 547.0667 (4.0 ppm).



***N*-benzyl-*N*-(3-((4-nitrophenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129g**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (94 mg, 0.274 mmol, 1 equiv.), triethylamine (115 µL, 83 mg, 0.822 mmol, 3 equiv.), and 4-nitrobenzenesulfonyl chloride (64 mg, 0.288 mmol, 1.05 equiv.) to yield the title compound as a thick, colorless oil (112 mg, 0.228 mmol, 83%); R_f = 0.29 (DCM:EtOAc, 6:1); NMR spectra indicate the presence of two rotamers (ratio of 14.5:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ [8.29 (d, *J* = 8.9 Hz) & 8.08 (d, *J* = 8.8 Hz) & 7.89 (d, *J* = 8.5 Hz), Σ4H], [7.38 (s) & 7.32 – 7.26 (m) & 7.25 – 7.17 (m) & 7.12 (s) & 6.98 (dd, *J* = 7.5, 2.1 Hz) & 6.91 – 6.88 (m) & 6.82 (t, *J* = 6.5 Hz) & Σ15H], [4.59 (s) & 4.47 (s), Σ2H], [3.39 (t, *J* = 6.1 Hz) & 3.32 – 3.27 (m), Σ2H], [2.96 (q, *J* = 6.1 Hz) & 2.64 – 2.54 (m), Σ2H], [1.61 (p, *J* = 6.1 Hz) & 1.44 – 1.37 (m), Σ2H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 150.0, 146.6, 142.5, 136.0, 129.1 (+), 128.8 (+), 128.5 (+), 128.1 (+), 127.0 (+), 127.0 (+), 125.8 (+), 124.3 (+), 110.1 (+), 51.5 (–), 41.4 (–

), 40.2 (–), 31.9, 27.4 (–); FT IR (NaCl, cm^{-1}): 3145, 3103, 3064, 3029, 2933, 2866, 1608, 1529, 1445, 1426, 1207, 1152, 1093, 855, 737, 700, 610, 554; HRMS (TOF ES): found 514.1413, calculated for $C_{26}H_{25}N_3O_5S$ (M+Na) 514.1418 (1.0 ppm).



***N*-benzyl-*N*-(3-((((*1S*,*4R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide** (**129h**): The compound was prepared according to the typical procedure employing 3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium chloride (**163**) (250 mg, 0.729 mmol, 1 equiv.), triethylamine (305 μL, 221 mg, 2.19 mmol, 3 equiv.), and (1*S*)-(+)-10-camphorsulfonyl chloride (201 mg, 0.802 mmol, 1.1 equiv.) to yield the title compound as a thick, pale yellow oil (215 mg, 0.413 mmol, 57%); R_f = 0.31 (DCM:EtOAc, 3:1); NMR spectra indicate the presence of two rotamers (ratio of 3:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.41 (d, *J* = 4.9 Hz, 1H), 7.36 – 7.23 (m), 7.20 (dd, *J* = 9.2, 5.0 Hz), 7.17 – 7.09 (m), 6.98 – 6.94 (m), Σ12H], [5.82 (t, *J* = 6.5 Hz), 4.74 (t, *J* = 6.2 Hz), 4.69 – 4.57 (m), 4.52 (m), Σ3H], [δ 3.52 – 3.27 (m), 3.23 (d, *J* = 15.2 Hz), 3.18 (q, *J* = 6.4 Hz), 2.91 (d, *J* = 15.0 Hz), 2.86 – 2.73 (m), 2.40 (p, *J* = 3.3, 2.9 Hz), 2.36 (t, *J* = 3.8 Hz), 2.22 – 2.12 (m), 2.11 (t, *J* = 4.6 Hz), 2.04 (tq, *J* = 12.2, 4.2 Hz), 1.92 (d, *J* = 18.6 Hz), 1.84 (ddd, *J* = 14.3, 9.4, 4.8 Hz), 1.76 (tt, *J* = 10.6, 5.2 Hz), 1.46 (dddd, *J* = 29.4, 13.0, 7.8, 3.7 Hz), Σ15H], [1.07 (s), 1.00 (s), Σ3H], [0.89 (s), 0.88 (s,), Σ3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.3, 216.5, 175.3, 174.6, 143.3, 143.0, 137.6, 136.8, 129.0 (+), 128.8 (+), 128.7 (+), 128.7 (+), 128.3 (+), 127.8 (+), 127.5 (+), 127.0 (+), 126.8 (+), 126.7 (+), 126.6 (+), 126.1 (+), 110.8 (+), 110.2

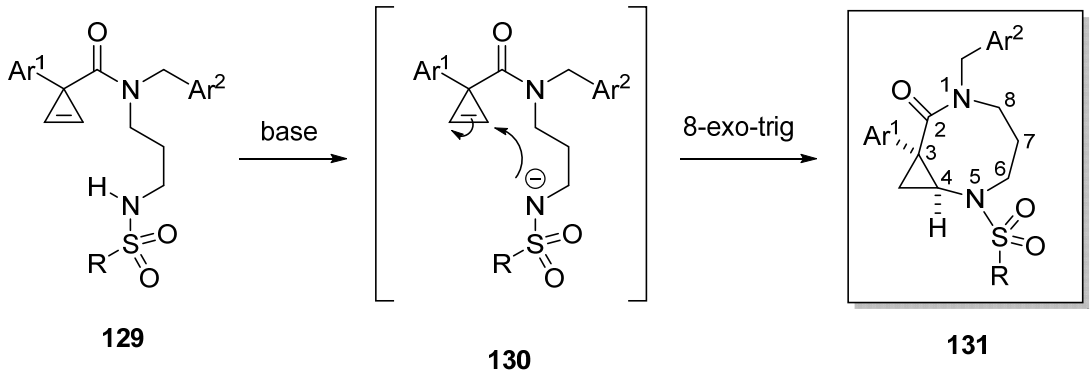
(+), 110.0 (+), 109.9 (+), 59.3, 59.0, 51.5 (–), 49.3 (–), 49.2 (–), 49.0, 48.6, 47.7 (–), 44.6 (–), 43.1 (–), 43.0 (–), 42.9 (+), 42.0 (–), 41.2 (–), 40.9 (–), 32.3, 32.1, 29.8 (–), 28.6 (–), 28.2 (–), 27.2 (–), 26.7 (–), 25.9 (–), 20.0 (+), 20.0 (+), 19.9 (+), 19.6 (+). FT IR (NaCl, cm^{-1}): 3281, 3205, 3148, 3103, 3060, 3028, 2958, 2887, 1743, 1645, 1618, 1446, 1424, 1329, 1146, 1067, 736, 700, 607, 567; HRMS (TOF ES): found 543.2292, calculated for $C_{30}H_{36}N_2O_4S$ (M+Na) 543.2294 (0.4 ppm).

Chapter 3. Strain-Release Activated Intramolecular Addition of Nitrogen Nucleophiles to 3,3-Disubtituted Cyclopropenes to Form 3,4-Cyclopropane-Fused 1,5-Diazocin-2-ones

3.1 Introduction

The previous chapter details the development of pronucleophilic synthetic precursors **129** for the base-assisted 8-*exo*-trig cyclization to form 3,4-cyclopropane-fused 1,5-diazocin-2-ones **131** (Scheme 52).

Scheme 52



Annulated cyclopropane moieties can be found in marketed drugs such as broad spectrum antibiotic Trovafloxacin and the oral anti-diabetic Saxagliptin (Figure 8), as well as drug candidates like the anti-HCV BMS-791325. The cyclopropane moiety imparts rigidity to molecular scaffolds, allowing for the fixed spatial orientation of its substituents.[84] The development of new synthetic methods toward cyclopropane-annulated

target allows for the design of new drug candidates from unexplored chemical space which have the potential to operate via new modes of action and possess unique bioactivities.

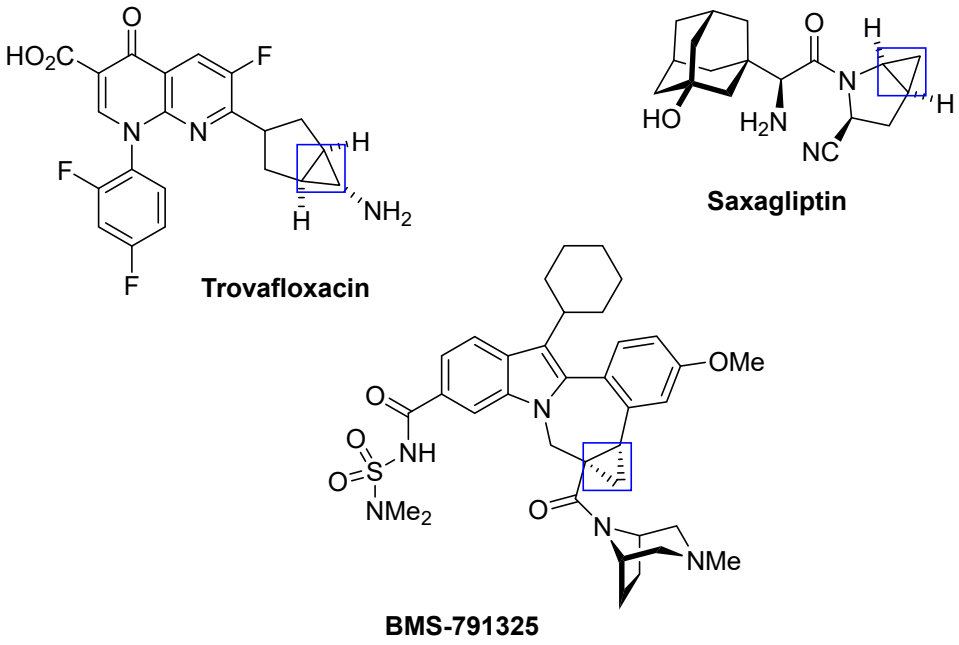
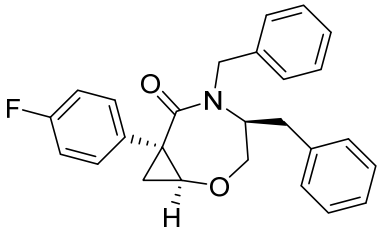


Figure 8: Marketed drugs and drug candidates featuring annulated cyclopropanes.

In our labs, annulated cyclopropanes which exhibit impressive biological activities have been synthesized. For example, cyclopropane-fused oxazepanone shown in Figure 9 exhibited promising activity against *Mycobacterium abscessus* with apparent low general toxicity against cultured human cells.[58]



MIC: 50 ± 2.3 μM
IC_{50} = 3.13 ± 0.04 μM

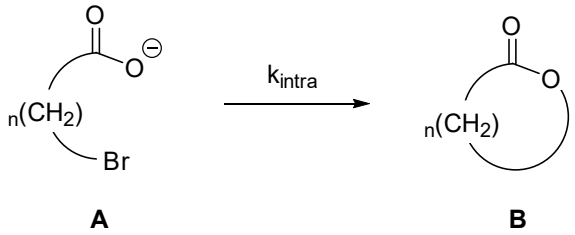
Figure 9: A cyclopropane-fused oxazepanone synthesized in our labs which possesses promising anti-mycobacterial activity.

The bioactivity of this example, and those similar in structure, warrant the further exploration of annulated cyclopropanes as potential drug candidates. In this chapter, a protocol for the effective synthesis of a novel class of 1,5-diazocin-2-ones – featuring 3,4-fusion to a cyclopropane moiety – is described.

3.2 Origins of Difficulty in the Direct Cyclization of Medium-Sized Rings

Although perhaps the most straightforward route to medium-sized (7- to 11-membered) cycles, the direct cyclization of such systems is inherently difficult. This is due to both entropic and enthalpic factors present both in the transition states and in the final products of such transformations – i.e. reflective of $\Delta G^{\ddagger}$ and ΔG, respectively. The seminal work by Mandolini[14] in 1986 offers a thorough analysis of the kinetics and thermodynamics of simple cyclization systems of varying ring size, and in turn provides explanations of these phenomena. The lactonization of ω-bromoalkanoate anions (Scheme 53) provides a simple model for cyclizations affording cyclic carboxylic acid derivatives and is one for which a nearly complete set of experimental data is available.

Scheme 53



A **B**

The rates of cyclization are highly dependent on the number of members in the forming cycle (Figure 10); with differing dominating factor(s) depending on whether small-, medium-, or large-sized rings are considered. A common theme, however, is the amount of ring strain associated with the transition states and the products of cyclization (Figure 11). The lactonizations of small (particularly 3-membered) systems exhibit low

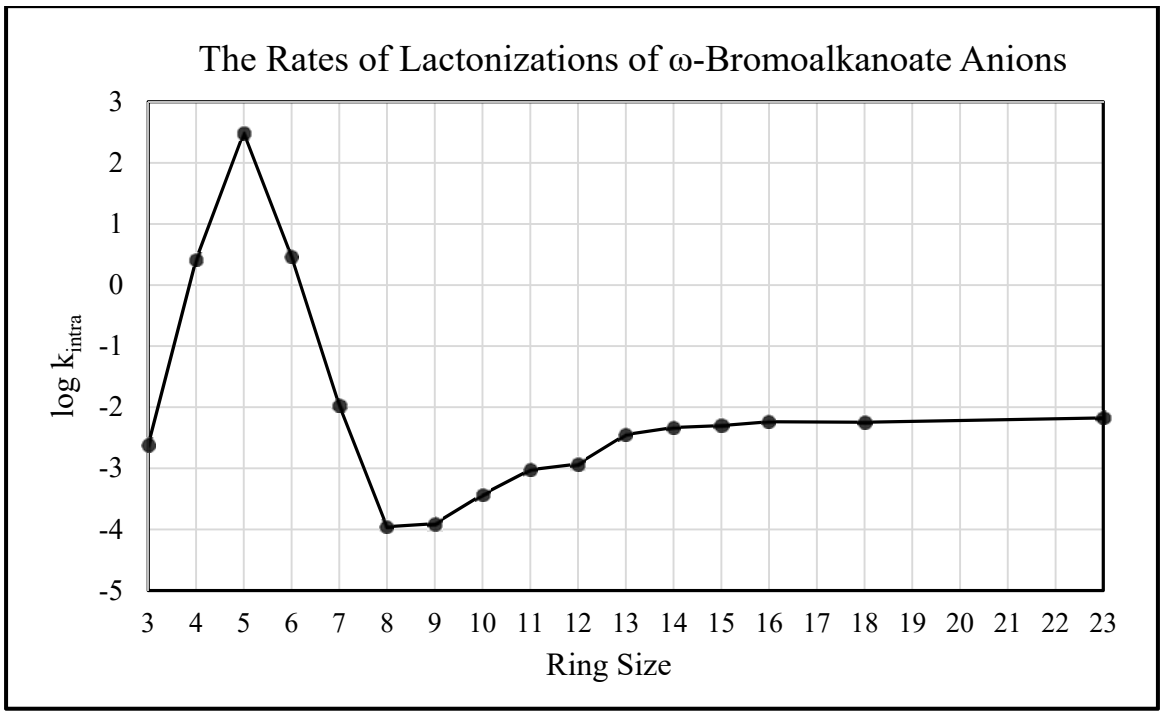


Figure 10: Experimental rate constants of the lactonization of ω-bromoalkanoate anions in 99:1 DMSO:H_2O at 50 °C.

rates of intramolecular reaction when compared to the rapid 5-membered lactonization due to the high degree of both angle and torsional strain (a.k.a. Baeyer and Pitzer strain, respectively) in the transition states and in the products. Homologous reactions of large (12-members and larger) systems exhibit reaction rates very close to that of the cyclization of the 3-membered lactone. Their increased flexibility allows for conformational adjustments which minimize both angle strain and torsional strain. Because of this, these large cycles incur only a very small enthalpic penalty in both the transition state and in the product. However, despite the relatively high level of conformational freedom present in the product, the high entropic cost imposed in the transition state has been shown to be most primarily responsible for the low reaction rates. Figure 10 shows a sharp decline into

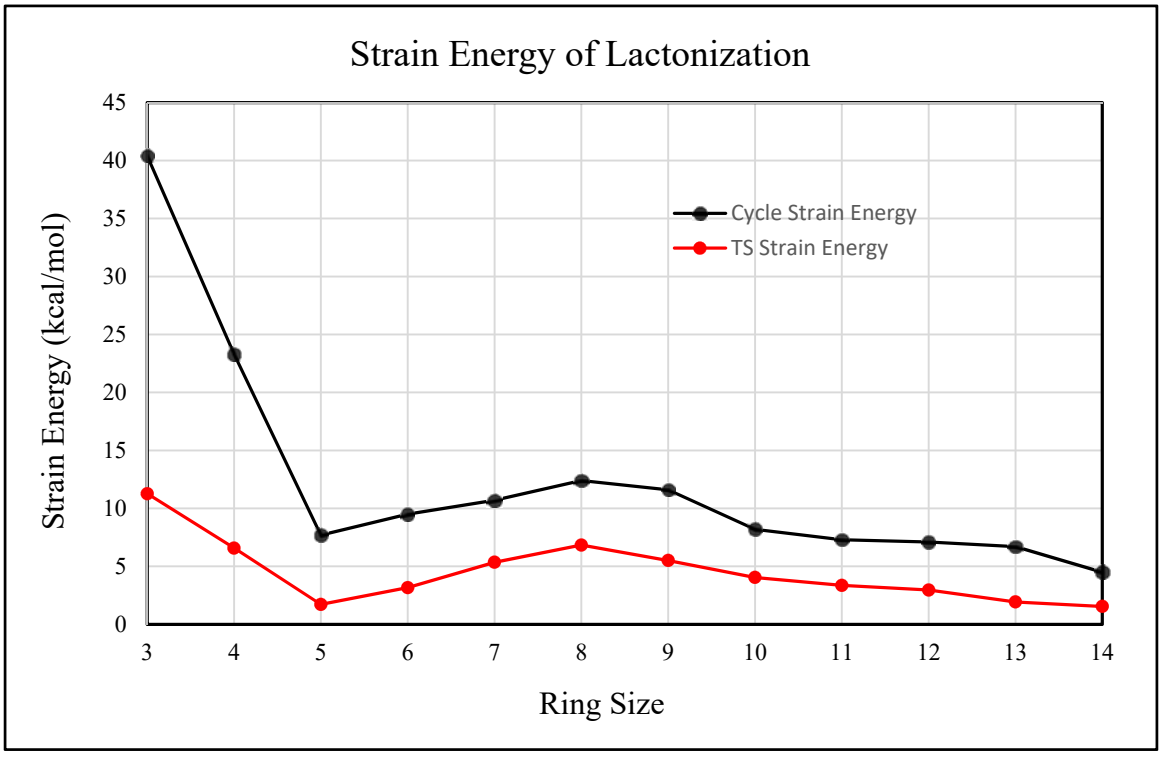


Figure 11: Experimental strain energies of the transition state and product cycles of the lactonization of ω-bromoalkanoate anions.

a kinetic valley appearing in the region of 7- to 11-membered cyclizations – the region corresponding to medium-sized rings. In this range, a third type of strain becomes important: transannular strain (a.k.a. Prelog strain). Transannular strain arises due to steric repulsion between substituents positioned across the ring system. The calculated lowest energy conformation of 8-membered oxocan-2-one is shown in Figure 12. Interactions of H-1 with H-3, and of H-2 with H-3, are prime examples of transannular strain. In both cases, the hydrogens are involved in destabilizing steric interactions across the ring which are not present to a significant degree in small- or large-sized cycles in their lowest energy conformations. Any relief of transannular strain by way of conformational adjustment results in increased torsional and/or angle strain.

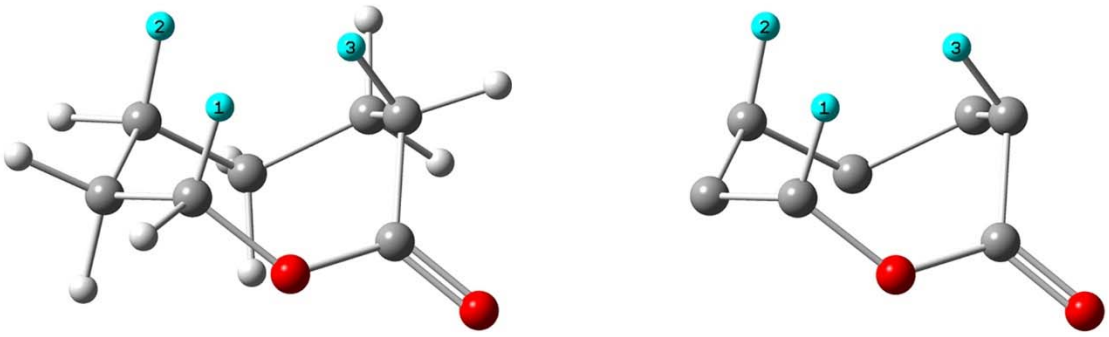


Figure 12: The transannular strain of oxocan-2-one. Several hydrogens on the right-most graphic are not shown for the purpose of clarity. Calculation: gas phase, ground state, geometry-optimized, (HF 6-311++G(d,p)) (see Appendix A1).[85]

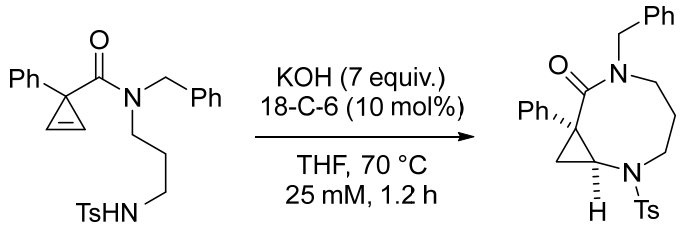
The high degree to which some combination of angle, torsional, and transannular strain is present in both the transition state and the product is unique to medium-sized rings and imposes a strong enthalpic cost on their formation. Further, a sizeable entropic cost also

accompanies the formation of these cycles in the transition state; although the medium-sized ring products themselves pay a significantly lower entropic penalty.[14]

3.3 Initial Reaction and Optimization of Reaction Conditions

The energy of the cyclopropene double bond is effective in mitigating the enthalpic difficulties inherent to the formation of 8-membered heterocycles. Employing conditions previously optimized in the Rubin group[72] for the intermolecular addition of sulfonamides to *in situ* generated conjugated cyclopropenes (Table 1, Entry 1), the 8-*exo*-trig cyclization of tosylsulfonamide **129d** was attempted (Scheme 54). The reaction

Scheme 54



129d **164d**, 79%

afforded a single major compound. The isolated product was analyzed by 1D and 2D NMR to confirm the structure (See Appendix 3). It was confirmed that primary sulfonamide **129d** was successfully cyclized to afford 1,5-diazocin-2-one **164d** in good yield (79%) in just over an hour at 70 °C.

We believe this cyclization to take place in a metal-templated fashion (Figure 13) wherein a potassium cation – supplied by the base – coordinates to the carbonyl oxygen,

the cyclopropene π-bond, and the anionic nucleophile, arranging the members of the forming cycle into a cyclic array, thereby lowering the energy of the transition state and facilitating the reaction.

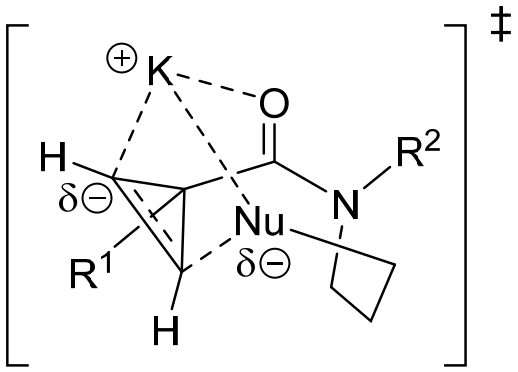
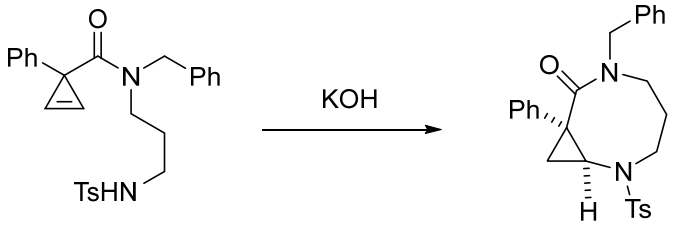


Figure 13: Proposed potassium-templated transition State

The successful synthesis of diazocine **164d** prompted the optimization of reaction conditions (Table 1). The phase transfer catalyst (18-crown-6) was found to have no observable effect on the reaction under these conditions and therefore was deemed to be unnecessary. A reduction in reaction temperature from 70 °C to 50 °C resulted in longer reaction times and slightly higher yield (Table 1, Entry 3). The remainder of optimization reactions were allowed to run over the course of 14 hours (overnight) as a matter of convenience. The reaction performed well in ethereal solvents in general (Table 1, Entries 3-6) while providing dissatisfactory yields in more polar aprotic solvents (Table 1, Entries 7-9). The reaction yield suffers slightly in toluene (Table 1, Entry 10). DMSO and DMF provided particularly low yields after 14 hours, despite full conversion being achieved. It is rationalized here that the ability of such solvents to solvate the potassium cation disrupts the formation of the necessary cyclic transition state (see Figure 13), while ethereal and

Table 1: Optimization of reaction conditions for the formation of diazocinone 242a.



129d **164d**

Entry	18-crown-6 (mol %)	Time (h)	Solvent	Temperature (°C)	Equiv. KOH	Concentration (mM)	Yield[a] (%)
1	10	1.2	THF	70	7	25	79
2	0	1.2	THF	70	7	25	79
3	0	6.5	THF	50	7	25	82
4	0	14	1,4-dioxane	50	7	25	83
5	0	14	DME	50	7	25	80
6	0	14	MTBE	50	7	25	77
7	0	14	DMSO	50	7	25	32
8	0	14	DMF	50	7	25	54
9	0	14	MeCN	50	7	25	67
10	0	14	toluene	50	7	25	70
11	0	14	THF	50	5	25	85
12	0	14	THF	50	4	25	89
13	0	14	THF	50	2	25	94
14	0	14	THF	50	1	25	IC[b]
15	0	14	THF	50	2	12.5	95
16	0	14	THF	50	2	37.5	95
17	0	14	THF	50	2	50	95

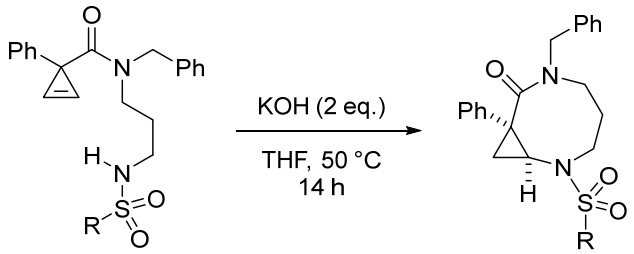
[a]NMR yields employing dibromomethane as the internal calibrant. [b]Reaction proceeded with incomplete conversion of starting material.

hydrocarbon solvents are much less able to solvate the cation and therefore permits its formation to a much higher degree. As the base loading was systematically varied, it was found that the addition of fewer equivalents of potassium hydroxide, to a point, was accompanied by increased yields (Table 1, Entries 11-14). It is possible that partial hydrolysis of the sulfonamido group competes with the cyclization. Employing only a single equivalent of base resulted in incomplete conversion of the starting material (Table 1, Entry 14). The increase or decrease of the reaction concentration was proved to have no significant effect on the yield (Table 1, Entries 15-17). A maximum yield of 95% was achieved.

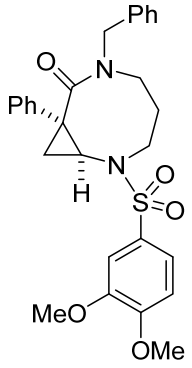
3.4 Synthesis of 3,4-Cyclopropane-Fused 1,5-Diazocin-2-ones via 8-*exo*-trig Cyclization

With optimized reaction conditions in hand, the synthesis of several examples of diazocinones **164** was carried out (Figure 14). 3,4-Dimethoxyphenyl cyclic sulfonamide **164a** – possessing the most electron-donating sulfonamido group of the series – provided the highest isolated yield of 93%. Similarly high yields were obtained in the cases of **164b, 164c, 164d,** and **164e**. Compound **164f** – bearing the slightly electron withdrawing *p*-bromophenyl sulfonamido group – saw a significant decline in yield. In the case of *p*-nitrophenyl cyclic sulfonamide **164g**, the reaction required 20 hours (in contrast to the normal 14 hours) to proceed to completion. This reaction provided the lowest yield of the series. Thus, cyclization precursors **129** bearing electron-donating or groups that are relatively neutral in this regard, produce higher yields than those bearing electron-

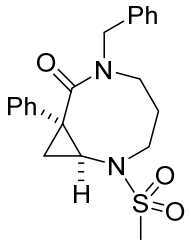
Figure 14: 1,5-Diazocin-2-ones synthesized via 8-*exo*-trig cyclization.



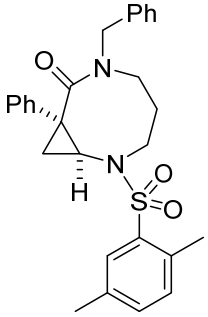
129 **164**



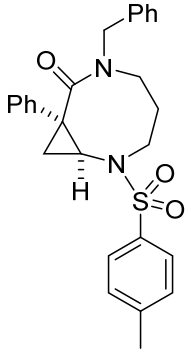
164a, 93%



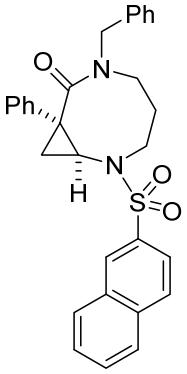
164b, 92%



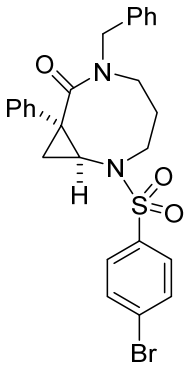
164c, 87%



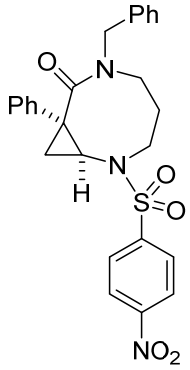
164d, 91%



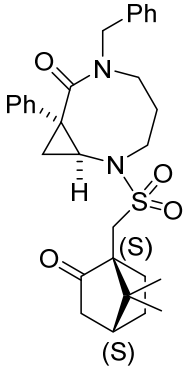
164e, 90%



164f, 79%



164g, 31%



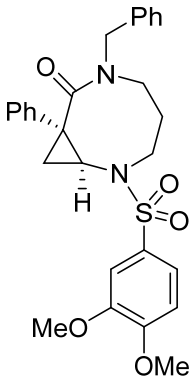
164h, 90%
~1:1 dr

withdrawing groups. Example **164h** was derived from enantiopure (+)-camphorsulfonyl chloride, but provided no significant diastereoselectivity (~1:1 by NMR) and produced a preparatively inseparable mixture of diastereomers. The mixture was inseparable via analytical HPLC as well. The lack of selectivity is reasonable as the stereogenic centers of the camphorsulfonyl group are quite remote to the site of nucleophilic attack and therefore cannot induce a large difference in the energies of the two possible diastereomeric transition states.

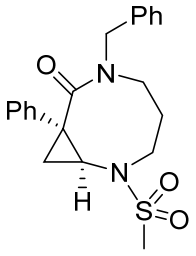
3.5 Conclusion

1,5-Diazocin-2-ones **164** represent the first known class of such azalactams featuring fusion to a cyclopropane ring. With the unique structural features imparted by the fused cyclopropane moiety comes the possibility of unique biological activity and/or enhanced bioactivity of analogous diazocines which lack this cyclopropane fusion. The sulfonyl functional groups of the cycles were varied, showing that strongly electron withdrawing groups negatively affect the yields of these cycles. Further diversification of these diazocines via the variation of Ar^1 and/or Ar^2 was not explored and is a subject of future research.

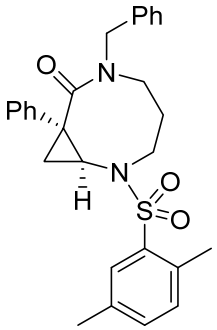
3.6 Experimental



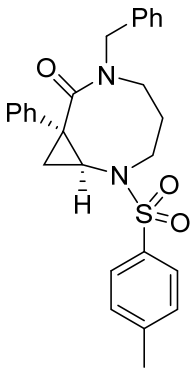
(*1S,*8S**)-6-Benzyl-2-((3,4-dimethoxyphenyl)sulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164a**): Typical Procedure: A 5 mL oven-dried v-vial equipped with a magnetic spin vane was charged with *N*-benzyl-*N*-(3-((4-methylphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129a**) (19.5 mg, 0.038 mmol, 1 equiv.), freshly-ground potassium hydroxide (4.3 mg, 0.077 mmol, 2 equiv.), and dry THF (800 μL). The reaction mixture was stirred overnight (14 h) at 50 °C. The reaction mixture was allowed to cool RT and passed through a short plug of silica eluting with EtOAc. Solvent was removed from the resulting solution via rotary evaporation. The product was purified by column chromatography on silica gel eluting with hexanes:EtOAc (2:3) to afford the title compound as a white solid (18.1 mg, 0.036 mmol, 93%); R_f = 0.35 (hexanes:EtOAc, 2:3); mp 194-198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.47 (dd, J = 8.4, 2.1 Hz, 1H), 7.34-7.17 (m, 9H), 7.12 (dd, 7.2, 1.7 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 5.31 (d, J = 14.8 Hz, 1H), 4.16 (dt, J = 14.0, 3.6 Hz, 1H), 4.04 (d, *J* = 14.9 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.68 (dd, *J* = 15.7, 10.9 Hz, 1H), 3.05 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.77-2.65 (m, 3H), 1.95 (dtd, *J* = 15.8, 11.5, 4.6 Hz, 1H), 1.60-1.50 (m, 1H), 1.33 (p, *J* = 5.6 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 169.3, 153.9, 149.3, 138.7, 137.5, 129.5, 129.0 (+), 128.7 (+), 128.4 (+), 127.6 (+), 127.2 (+), 125.5 (+), 121.7 (+), 110.9 (+), 110.4 (+), 56.5 (+), 56.4 (+), 53.5 (–), 49.3 (–), 46.6 (+), 46.0 (–), 28.3 (–), 23.9 (–); FT IR (NaCl, cm^{-1}): 3060, 3027, 2965, 2934, 2848, 1641, 1587, 1509, 1441, 1346, 1263, 1140, 1020, 733, 702, 573; HRMS (TOF ES): found 529.1778, calculated for $C_{28}H_{30}N_2O_5S$ (M+Na) 529.1773 (0.9 ppm).



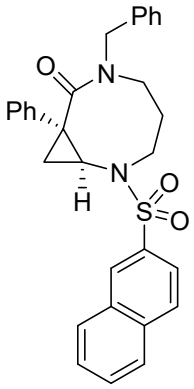
(*1S,*8S**)-6-Benzyl-2-(methylsulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164b**): The compound was prepared according to the typical procedure employing *N*-benzyl-N-(3-(methylsulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129b**) (32.7 mg, 0.085 mmol, 1 equiv.) and freshly-ground potassium hydroxide (9.5 mg, 0.170 mmol, 2 equiv.) to yield the title compound as a white crystalline solid (30.2 mg, 0.079 mmol, 92%). R_f = 0.23 (hexane:EtOAc:MeOH, 6:3:1, 0.2% TFA); mp 131 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 8H), 7.19 – 7.15 (m, 2H), 5.28 (d, *J* = 15.4 Hz, 1H), 4.19 (dt, *J* = 14.2, 3.8 Hz, 1H), 4.11 (d, *J* = 14.7 Hz, 1H), 3.79 (dd, *J* = 15.5, 11.0 Hz, 1H), 3.17 – 3.11 (m, 2H), 3.05 (ddd, *J* = 15.0, 12.4, 3.0 Hz, 1H), 2.93 (s, 3H), 2.59 (dd, *J* = 7.1, 5.3 Hz, 1H), 2.00 – 1.87 (m, 1H), 1.67 – 1.57 (m, 1H), 1.49 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 138.2, 137.0, 129.2 (+), 128.9 (+), 128.6 (+), 127.9 (+), 127.4 (+), 125.4 (+), 52.9 (–), 49.6 (–), 46.6 (+), 46.3 (–), 38.2 (+), 36.6, 28.2 (–), 23.4 (–); FT IR (NaCl, cm^{-1}): 3083, 3060, 2923, 2907, 2850, 1701, 1638, 1446, 1350, 1167, 823, 745, 700, 614, 580, 542; HRMS (TOF ES): found 407.1388, calculated for $C_{21}H_{24}N_2O_3S$ (M+Na) 407.1405 (4.2 ppm).



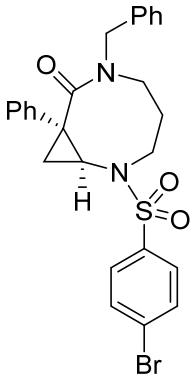
(*1S*,8S)-6-Benzyl-2-((2,5-dimethylphenyl)sulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164c**): The compound was prepared according to the typical procedure employing *N*-benzyl-*N*-(3-((2,5-dimethylphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129c**) (28.3 mg, 0.060 mmol, 1 equiv.) and freshly-ground potassium hydroxide (6.7 mg, 119 mmol, 2 equiv.) to yield the title compound as a white crystalline solid (24.7 mg, 0.052 mmol, 87%); R_f = 0.33 (hexanes:EtOAc:MeOH, 7:2:1); mp 182-185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 2.0 Hz, 1H), 7.35-7.19 (m, 10H), 7.16 (dd, *J* = 7.4, 1.8 Hz, 2H), 5.43 (d, *J* = 14.7 Hz, 1H), 4.37 (dt, *J* = 14.6, 3.8 Hz, 1H), 3.90 (d, *J* = 14.7 Hz, 1H), 3.74 (dd, *J* = 15.7, 11.0 Hz, 1H), 3.16 (dd, *J* = 8.0, 5.4 Hz, 1H), 3.11 – 2.99 (m, 2H), 2.59 (s, 3H), 2.41 (s, 3H), 1.98 – 1.83 (m, 2H), 1.68 – 1.58 (m, 2H), 1.19 (dd, *J* = 8.0, 6.7 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ ppm 169.4, 138.6, 137.3, 136.6, 136.2, 135.3, 134.4 (+), 133.0 (+), 131.1 (+), 129.0 (+), 128.8 (+), 128.5 (+), 127.7 (+), 127.1 (+), 125.5 (+), 51.7 (–), 48.9 (–), 46.3 (+), 45.7 (–), 36.5, 28.0 (–), 23.3 (–), 21.0 (+), 19.9 (+); FT IR (NaCl, cm^{-1}): 3060, 3029, 2923, 1641, 1494, 1441, 1323, 1156, 821, 735, 713, 701, 588; HRMS (TOF ES): found 497.1876, calculated for $C_{28}H_{30}N_2O_3S$ (M+Na) 497.1875 (0.2 ppm).



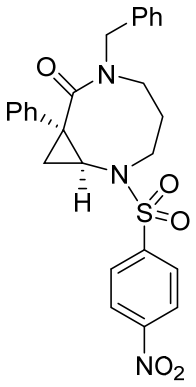
(*1S,*8S**)-6-Benzyl-8-phenyl-2-tosyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164d**): The compound was prepared according to the typical procedure employing *N*-benzyl-*N*-(3-((2,5-dimethylphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129d**) (25.0 mg, 0.054 mmol, 1 equiv.) and freshly-ground potassium hydroxide freshly-ground potassium hydroxide (6.1 mg, 0.109 mmol, 2 equiv.) to yield the title compound as a white solid (22.8 mg, 0.049 mmol, 91%); R_f = 0.36 (hexanes:EtOAc, 3:2); mp 172-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.74 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.33-7.16 (m, 8H), 7.12 (dd, *J* = 7.1, 1.8 Hz, 1H), 5.31 (d, *J* = 14.8 Hz, 1H), 4.16 (dt, *J* = 13.9, 3.4 Hz, 1H), 4.06 (d, *J* = 14.8 Hz, 1H), 3.67 (dd, *J* = 15.6, 11.0 Hz, 1H), 3.06 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.74-2.62 (m, 3H), 2.46 (s, 2H), 1.97 (dtd, *J* = 15.7, 11.9, 4.6 Hz, 1H), 1.55 (ddt, *J* = 14.8, 5.6, 2.4 Hz, 1H), 1.36 (dd, *J* = 7.1, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 144.1, 138.8, 137.6, 134.8, 130.1 (+), 129.0 (+), 128.8 (+), 128.5 (+), 127.9 (+), 127.7 (+), 127.2 (+), 125.6 (+), 53.6 (–), 49.4 (–), 46.8 (+), 46.1, 36.7, 28.4 (–), 23.9 (–), 21.8 (+); FT IR (NaCl, cm^{-1}): 3061, 3030, 2961, 2924, 2855, 1641, 1598, 1495, 1479, 1442, 1425, 1380, 1344, 1165, 1129, 1090, 816, 734, 712, 699, 563, 551, 541; HRMS (TOF ES): found 483.1721, calculated for $C_{27}H_{28}N_2O_3S$ (M+Na) 483.1718 (0.6 ppm).



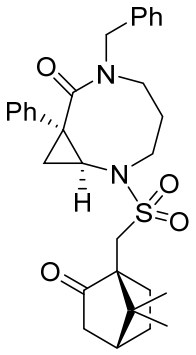
(*1S*,8S)-6-Benzyl-2-(naphthalen-1-ylsulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164e**): The compound was prepared according to the typical procedure employing *N*-benzyl-*N*-(3-(naphthalene-2-sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129e**) (26.7 mg, 0.054 mmol, 1 equiv.) and freshly-ground potassium hydroxide (6.0 mg, 0.108 mmol, 2 equiv.) to yield the title compound as a white crystalline solid (23.9 mg, 0.048 mmol, 90%); R_f = 0.38 (hexanes:EtOAc:MeOH, 7:2:1); mp 185-190 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.8 Hz, 1H), 7.92 (t, *J* = 7.8 Hz, 2H), 7.88 – 7.84 (m, 1H), 7.75 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.57 (dddd, *J* = 19.9, 8.0, 6.9, 1.3 Hz, 2H), 7.24 – 7.05 (m, 8H), 7.01 – 6.97 (m, 2H), 5.22 (d, *J* = 14.8 Hz, 1H), 4.16 (dt, *J* = 14.0, 3.8 Hz, 1H), 3.97 (d, *J* = 14.8 Hz, 1H), 3.58 (dd, *J* = 15.7, 11.0 Hz, 1H), 2.96 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.75 – 2.54 (m, 3H), 1.99 – 1.78 (m, 1H), 1.51 – 1.44 (m, 1H), 1.31 (dd, *J* = 7.9, 6.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 138.6, 137.5, 135.1, 134.8, 132.4, 129.6 (+), 129.5 (+), 129.2 (+), 129.2 (+), 129.0 (+), 128.8 (+), 128.5 (+), 128.2 (+), 127.9 (+), 127.6 (+), 127.2 (+), 125.5 (+), 122.9 (+), 53.7 (–), 49.3 (–), 46.7 (+), 46.0 (–), 36.8, 28.4 (–), 23.9 (–); FT IR (NaCl, cm^{-1}): 3060, 3041, 2965, 2855, 1641, 1598, 1447, 1442, 1425, 1360, 1344, 1165, 1090, 816, 734, 712, 699, 655, 563, 551, 541; HRMS (TOF ES): found 519.1748, calculated for $C_{30}H_{28}N_2O_3S$ (M+Na) 519.1718 (5.8 ppm).



(*1S*,8S)-6-Benzyl-2-((4-bromophenyl)sulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164f**): The compound was prepared according to the typical procedure employing *N*-benzyl-*N*-(3-((4-bromophenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129f**) (27.9 mg, 0.053 mmol, 1 equiv.) and freshly-ground potassium hydroxide (6.0 mg, 0.11 mmol, 2 equiv.) to yield the title compound as a white crystalline solid (22.0 mg, 0.042 mmol, 79%); R_f = 0.25 (hexanes:EtOAc:MeOH, 7:2:1); mp 151 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 4H), 7.35 – 7.18 (m, 8H), 7.14 – 7.10 (m, 2H), 5.29 (d, *J* = 14.8 Hz, 1H), 4.18 – 4.11 (m, 1H), 4.09 (d, *J* = 14.8 Hz, 1H), 3.69 (dd, *J* = 15.7, 11.0 Hz, 1H), 3.08 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.71 – 2.65 (m, 2H), 2.03 – 1.93 (m, 1H), 1.61 – 1.54 (m, 1H), 1.37 (dd, *J* = 6.9, 5.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 138.3, 137.3, 136.8, 132.7 (+), 129.3 (+), 129.1 (+), 128.8 (+), 128.5 (+), 128.4, 127.7 (+), 127.3 (+), 125.5 (+), 53.6 (–), 49.4 (–), 46.5 (–), 46.0 (–), 36.8, 29.9, 28.3 (–), 23.7 (–); FT IR (NaCl, cm^{-1}): 3087, 3061, 2920, 2850, 1703, 1640, 1445, 1349, 1167, 822, 745, 700, 609, 561; HRMS (TOF ES): found 547.0660, calculated for $C_{26}H_{25}BrN_2O_3S$ (M+Na) 547.0667 (1.3 ppm).



(*1S,*8S**)-6-Benzyl-2-((4-nitrophenyl)sulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164g**): The compound was prepared according to the typical procedure employing *N*-benzyl-*N*-(3-((4-nitrophenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129g**) (26.2 mg, 0.053 mmol, 1 equiv.) and freshly-ground potassium hydroxide (6.0 mg, 0.107 mmol, 2 equiv.) The reaction mixture was stirred for 24 hours at 50 °C. The target compound was obtained as a white crystalline solid (8.2 mg, 0.016 mmol, 31%); R_f = 0.26 (hexanes:EtOAc:MeOH, 6:3:1) mp 145 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.36 – 7.18 (m, 8H), 7.17 – 7.08 (m, 2H), 5.25 (d, *J* = 14.8 Hz, 1H), 4.22 – 4.16 (m, 1H), 4.12 (d, *J* = 14.8 Hz, 1H), 3.72 (dd, *J* = 15.7, 11.0 Hz, 1H), 3.10 (dd, *J* = 15.7, 6.2 Hz, 1H), 2.91 – 2.77 (m, 1H), 2.77 – 2.63 (m, 2H), 2.02 – 1.91 (m, 1H), 1.63 – 1.57 (m, 1H), 1.39 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 150.6, 143.9, 138.2, 137.3, 129.1 (+), 129.0 (+), 128.8 (+), 128.5 (+), 127.7 (+), 127.5 (+), 125.5 (+), 124.7 (+), 53.6 (–), 49.6 (–), 46.3, 46.0 (–), 37.0, 28.4 (–), 23.5 (–); FT IR (NaCl, cm^{-1}): 3052, 2926, 2852, 1701, 1640, 1530, 1446, 1377, 1350, 1163, 853, 737, 700, 609, 591; HRMS (TOF ES): found 514.1422, calculated for $C_{26}H_{25}N_3O_5S$ (M+Na) 514.1413 (1.8 ppm).



(*1S,*8S**)-6-Benzyl-2-((((*1S*,*4R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)-8-phenyl-2,6-diazabicyclo[6.1.0]nonan-7-one** (**164h**): A 5 mL oven-dried v-vial was charged with N-benzyl-N-(3-((3,4-dimethoxyphenyl)sulfonamido)propyl)-1-phenylcycloprop-2-ene-1-carboxamide (**129h**) (32.9 mg, 0.063 mmol, 1 equiv.), freshly-ground potassium hydroxide (7.1 mg, 0.126 mmol, 2 equiv.), and dry THF (1.3 mL). The reaction mixture was stirred overnight (14 h) at 50 °C. The reaction mixture was allowed to cool RT and passed through a short plug of silica eluting with EtOAc. Solvent was removed from the resulting solution via rotary evaporation. The product was purified by column chromatography on silica gel eluting with hexanes:EtOAc:MeOH (6:3:1) to afford the title compound as an inseparable mixture of diastereomers (~1:1) as a white solid (29.5 mg, 0.057 mmol, 90%); R_f = 0.25 (hexanes:EtOAc:MeOH, 6:3:1); mp 92-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 20H), 5.21 (dd, *J* = 22.0, 14.7 Hz, 2H), 4.10 (ddt, *J* = 19.2, 16.6, 3.6 Hz, 2H), 4.03 (d, *J* = 14.8 Hz, 1H), 3.97 (d, *J* = 14.8 Hz, 1H), 3.70 (ddd, *J* = 15.5, 10.9, 4.2 Hz, 2H), 3.41 (d, *J* = 14.6 Hz, 1H), 3.33 (d, *J* = 14.5 Hz, 1H), 3.27 (dd, *J* = 8.2, 5.3 Hz, 1H), 3.17 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.09 (ddd, *J* = 15.0, 12.4, 3.1 Hz, 1H), 3.06 – 2.97 (m, 3H), 2.90 (d, *J* = 14.6 Hz, 1H), 2.76 (d, *J* = 14.6 Hz, 1H), 2.67 (dd, *J* = 6.7, 5.3 Hz, 1H), 2.55 (dd, *J* = 7.0, 5.4 Hz, 1H), 2.47 (dddd, *J* = 21.6, 14.8, 11.8, 4.0 Hz, 2H), 2.35 (q, *J* = 4.0 Hz, 1H), 2.32 (q, *J* = 4.0 Hz, 1H), 2.06 (q, *J* = 4.3 Hz, 2H), 2.00 (tq, *J* = 12.2, 4.4 Hz, 2H), 1.91 (d, *J* = 5.2 Hz, 1H), 1.87 (d, *J* = 5.3 Hz, 1H), 1.62 (dddd, *J* = 14.0, 9.3, 7.1, 4.7 Hz, 4H), 1.50 (dddd, *J* = 11.3, 8.6, 6.4, 3.1 Hz, 2H), 1.42 – 1.33 (m, 4H), 1.09 (s, 3H), 1.07 (s, 3H), 0.85

(d, J = 2.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.8, 215.8, 169.5, 169.3, 138.8, 138.8, 137.6, 137.5, 129.0 (+), 128.7 (2C, (+)), 128.5 (+), 127.6 (2C, (+)), 127.1 (+), 125.5 (+), 125.4 (+), 58.8, 58.7, 53.7 (–), 53.1 (–), 49.4 (–), 49.1 (–), 48.4, 48.1, 46.7 (–), 46.6 (+), 46.3 (+), 46.2 (–), 46.0 (–), 43.0 (+), 42.9 (+), 42.8 (–), 36.7, 36.5, 28.6 (–), 28.3 (–), 27.1 (2C, (–)), 25.5 (2C, (–)), 23.6 (–), 23.3 (–), 20.2 (+), 20.1 (+), 20.0 (+); FT IR (NaCl, cm^{-1}): 3060, 3028, 2961, 1745, 1640, 1496, 1480, 1342, 1052, 757, 699, 562, 526. HRMS (TOF ES): found 543.2291, calculated for $C_{30}H_{36}N_2O_4S$ (M+Na) 543.2294 (0.6 ppm).

Appendix

A1. Hartree-Fock Computations of Oxocan-2-one

The *ab initio* ground state geometry optimization and energy calculations of oxocan-2-one were performed using restricted Hartree-Fock employing a as basis set of 6-311++G(d,p)).

Energy: -421.891991122 a.u.

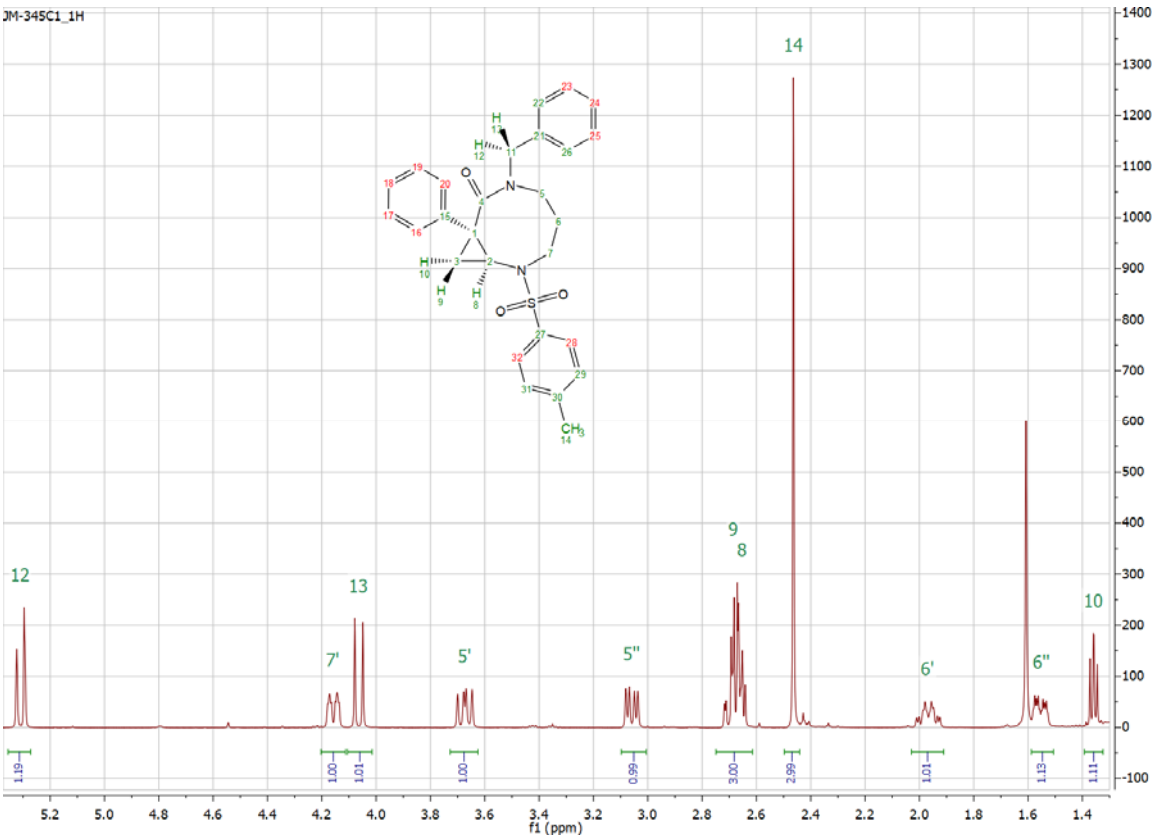
Z-matrix of oxocan-2-one:

C	1.43376569	-0.37089891	-0.04441113
C	0.98518472	0.70421237	0.93409465
C	0.26726831	1.85590377	0.21987702
C	-0.89275971	1.40744519	-0.68181081
C	-1.94312826	0.54516694	0.03598411
C	-1.80041813	-0.96837317	-0.19432286
C	-0.59524293	-1.65212469	0.45100201
O	0.59953969	-1.42953933	-0.24823778
O	2.48711853	-0.26131536	-0.63797200
H	1.90229829	1.11210344	1.42415200
H	0.38681545	0.32534972	1.78565390
H	1.00577699	2.41665684	-0.40379104

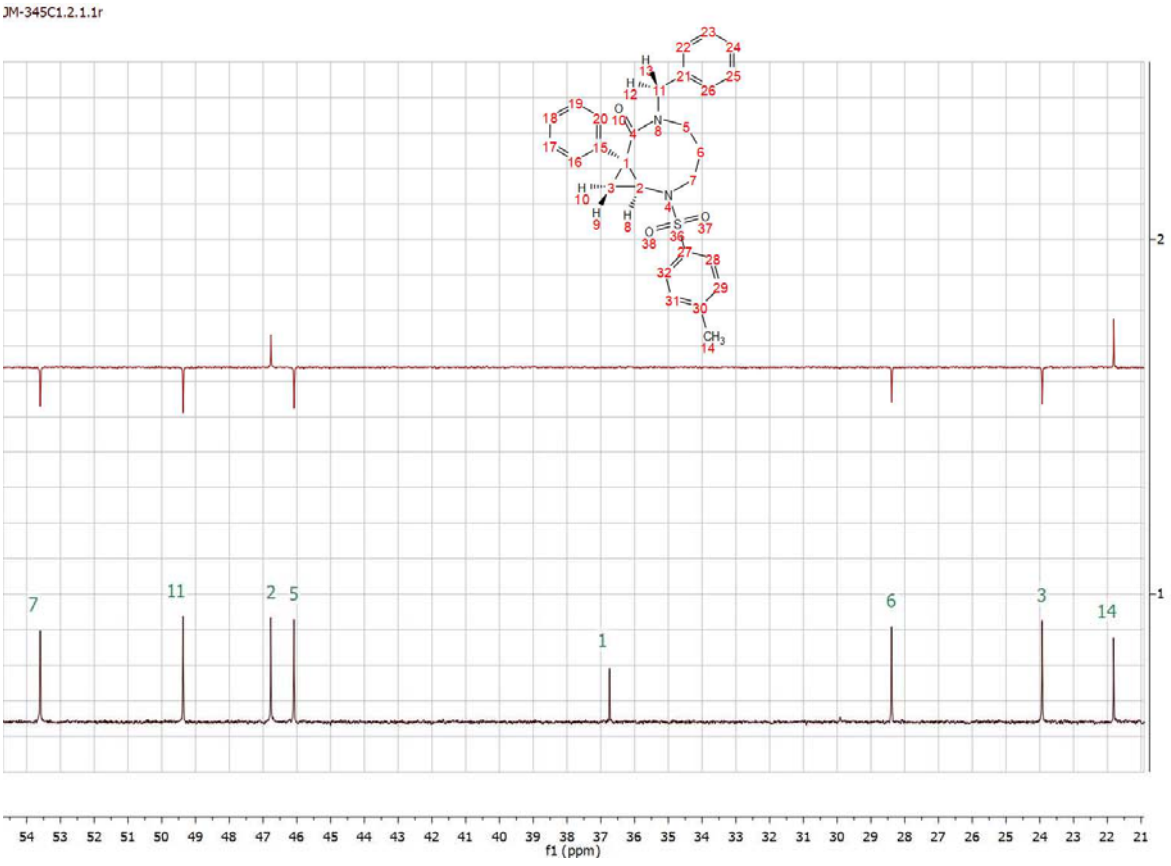
H	-0.11348389	2.57574359	0.98441366
H	-1.38373970	2.33322119	-1.07188643
H	-0.50765766	0.87309877	-1.58086578
H	-1.96690205	0.77545337	1.12578441
H	-2.94957934	0.83841592	-0.35545831
H	-1.81446968	-1.18591074	-1.28893475
H	-2.71861814	-1.45214738	0.22454216
H	-0.76514284	-2.75529879	0.38662630
H	-0.49658129	-1.45783740	1.53696419

A2 Structure Determination of 164d

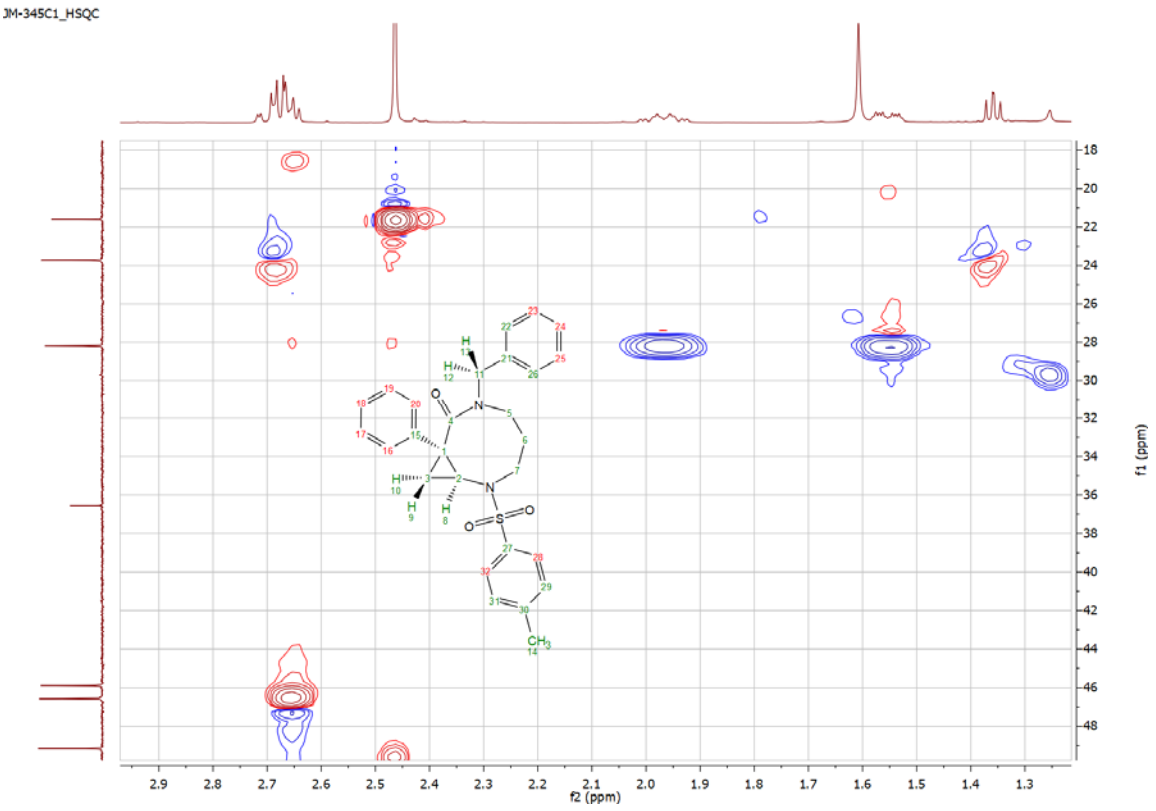
^{1}H and ^{13}C NMR spectra show no evidence of rotational isomers, as is expected when rotation around the amide bond is no longer possible. Instead magnetically non-equivalent signals appear for all aliphatic protons. Each pair of protons on each methylene carbon of the propylene chain (C6, C6, C7) are pairs of diastereotopic protons, indicating fixed geometries which are consistent with their presence in a ring system.



Below, the aliphatic region of the DEPT-135 (top) and ^{13}C (Compound Pulse Decoupled) (bottom) are stacked and confirm the presence of five CH_2 groups, two (+) signals in DEPT-135 indicating methine or methyl carbons, and one signal which appears in the ^{13}C but not in the DEPT indicating a fully substituted carbon – each magnetically non-equivalent. This is also supportive of the structure shown.



HSQC data indicate the presence of the 1,1,2-trisubsituted system of compound **164d**. One-bond C-H interactions exist for carbon C3 (23.9 ppm) with both protons H9 (2.69 ppm) and H10 (1.36 ppm) with. A one-bond C-H interaction exists for C3 (46.8 ppm) and proton H8 (2.65 ppm).



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